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## Original Communications

### THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN ACUTE POLIOMYELITIS

#### PRELIMINARY REPORT

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THE purpose of this paper is (1) to describe clinical observations of the sympathetic nervous system involvement in acute anterior poliomyelitis, (2) to record briefly the presumptive evidence, (3) to present conclusive evidence that angiospasm exists in the acute stage of poliomyelitis and may be responsible for muscle spasm and pain, and (4) to suggest practical methods for relief of pain and spasm.

#### CLINICAL OBSERVATIONS OF SYMPATHETIC NERVOUS SYSTEM INVOLVEMENT

*A. In the Cervical Region.*—Paralysis of the cervical sympathetic is either extremely rare or else it is mistaken for facial paralysis, and is classified, therefore, as polioencephalitis. Since 1928 we have seen three such cases. The muscle paralyses were different in each case. However, the symptoms relating to Horner's syndrome were the same: ptosis, or narrowing of the palpebral fissure; enophthalmos, or retraction of the eyeball; contraction of the pupil on the affected side; flushing of the face due to the dilatation of the blood vessels; and anhidrosis, or absence of sweating.

*B. In the Thoracic Region.*—The thoracic portion of the sympathetic may be diseased; the symptoms in this condition, being mainly visceral, are less easily recognized.

Our patient with thoracic sympathetic involvement was a boy aged 14 years, well developed and well nourished, who suddenly complained of occipital headache. On the following day the headache spread to the temporal regions. The temperature rose to 101° F. The family doctor diagnosed the condition as "grippe." The next morning the patient was unable to support his head or flex his forearms. The diagnosis was then changed to poliomyelitis and he was admitted to the Kingston Avenue Hospital.

*Physical examination:* On admission to the hospital the temperature was 101° F., pulse 120. The heart sounds were irregular; there were no murmurs.

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Read before the clinicopathological conference at Kingston Avenue Hospital for Communicable Diseases, Brooklyn, N. Y., June 3, 1948.

The chest revealed wheezes and rhonchi on auscultation, but no fine râles. There were no dull areas on percussion. His face was cyanotic. A blotchy purplish macular eruption was noted on the chest and shoulders. He was dyspneic.

*Neurological examination:* There was no evidence of cranial nerve involvement. The arches of the soft palate were symmetrical; the uvula was in the midline; the soft palate moved freely. The tongue on protrusion deviated neither to the left nor to the right and was freely movable. There was no stagnant mucus about the pillars, and none on the posterior pharyngeal wall. He did not cough. His voice was clear and he pronounced the consonant *B* sharply and distinctly. He drank fluids and swallowed semisolid food without difficulty. Respirations were shallow and rapid and occasionally they were deep and slow. The alae nasi dilated with inspiration. The diaphragm moved freely and the abdominal reflexes were present. His neck was not stiff. He was unable to flex his forearms and could not support his head. He was mentally clear, cooperated willingly, but was frightened. His eyes were wide open. His face was cyanotic, his lips were cherry red, and he perspired profusely. He had one complaint, "I cannot get my breath."

From the clinical picture it was evident that this patient had neither bulbar poliomyelitis nor respiratory muscle paralysis. However, because of the extreme cyanosis and shortness of breath, the admitting physician placed him in the respirator. He showed marked improvement in the respirator for a short period of time. The cyanosis cleared, the lips became pink. However, he did not synchronize with the machine and had to be taught to do so. He tried very hard to breathe with the respirator but failed. His face soon became cyanotic and his lips dark red. He continued to complain that he could not get his breath. It was evident that he was suffering from hypoxia. Something was preventing the oxygen from reaching the red cells in the blood. The respiratory tract was investigated. The patient was laryngoscoped and the vocal cords were seen to move freely; there were no polyps, ulcers, nor edema about the larynx. The patient was examined bronchoscopically and no mucus plugs either in the trachea or bronchi were seen. Roentgen examination showed the lung fields to be clear. On the assumption that he had bronchiolar spasm, the patient was given epinephrine subcutaneously without any response. Having failed to discover an obstruction in the laryngotracheobronchial tract, the patient was given oxygen by mask without results. Oxygen by nasal catheter at the rate of 10 to 15 L. per minute was substituted. The oxygen thus delivered apparently failed to reach the blood for his face remained cyanotic and he continued to complain that he could not get his breath. The temperature rose to 104° F. and the pulse dipped to 90. He became comatose and died thirty-six hours after admission, with oxygen flowing through the catheter into the bronchial tree.

We felt that the cause of death in this case was probably due to spasm of the pulmonary blood vessels. Purves Stewart<sup>1</sup> regards the vasoconstriction of the pulmonary vessels, with the transient dilatation and irregularity

of the right heart met with in certain gastric and hepatic disorders (and seen by us in this case of poliomyelitis), as an affection of the thoracic portion of the sympathetic nervous system.

The clinical picture of pulmonary angiospasm very closely simulates the signs and symptoms of bulbar poliomyelitis and sometimes the patient is tracheotomized unsuccessfully.

*C. In the Gastric Region.*—Sympathetic nervous system involvement either directly or reflexly may produce transient vomiting for which no explanation can be found. The vomiting may begin with the onset of poliomyelitis or during the first few days of the disease. Repeated lumbar punctures do not offer any relief. This vomiting is probably due to a transient pylorospasm.

*D. In the Intestinal Region.*—Involvement of the sympathetic nervous system may manifest itself either by constipation or diarrhea. Most of our patients were constipated and required attention in the form of frequent enemas. Grulee and Panos<sup>2</sup> met with similar experiences. However, Ivan Wickman<sup>3</sup> states that in his series of cases diarrhea was more common than constipation. The stools may be watery, green, and fetid. Spastic constipation with its hard, dry stools, and also mucous colitis with its paroxysms of increased peristalsis accompanied by an excessive secretion of intestinal mucus, are probably both evidences of vagotonus. The apparent contradiction in ascribing constipation and diarrhea to the same cause is explained by the fact that in one condition the circular fibers of the intestine are affected, producing constipation, while in the other the longitudinal fibers are affected, causing diarrhea.

*E. In the Rectal Region.*—Some of our patients showed evidence of chronic intestinal obstruction as a result of sphincter spasm. Their abdomens became distended both by gas and feces and assumed barrel-like shapes. Rumbling and gurgling were heard and felt. The feces had to be removed mechanically from their rectums.

*F. In the Bladder Region.*—Sympathetic nervous system involvement may disturb the normal function of the bladder. The bladder has a double innervation, partly from the sympathetic and partly from the parasympathetic. The sympathetic reflex center is situated in the lateral horn of the spinal cord in the region of the third, fourth, and fifth lumbar vertebrae. The parasympathetic nerves reach the bladder via the second, third, and fourth sacral roots. Involvement of the sympathetic nerves causes increased tonus of the sphincter and dilatation of the bladder with retention of urine. Involvement of the parasympathetic nerves produces relaxation of the sphincter and contraction of the bladder or incontinence of urine. Bladder involvement is not uncommon when both lower extremities are paralyzed. Retention of urine seems to be more common than incontinence. Twenty-two patients in our series had retention of urine and only one had incontinence.

*G. In the Skin.*—Involvement of the sympathetic nervous system in the skin may reveal itself in different ways:

1. *Profuse sweating:* Sweating is an early sign and can be found in nearly all poliomyelitis cases. Sometimes the patients continue to perspire for weeks

after the acute phase has subsided. There seems to be no relationship between the height of the temperature and the sweating.

2. *Tache spinale*: While stroking the skin to elicit abdominal and cremasteric reflexes we occasionally noticed: (a) the appearance of a pink streak which in some cases would fade within three to five minutes; (b) when muscle weakness or sluggish reflexes were present the streaks would assume a purple hue and remain up to ten minutes; or (c) not infrequently the streaks would appear cyanotic and would linger up to one-half hour before they would fade into normal skin color. The length of time required for the cyanotic tache to fade impressed us very much. It was evident that there was interference in the blood circulation to the part in question.

3. *Angioparesis in the skin*: Skin eruptions have been observed during the first few days and sometimes later in the disease. The exanthemas may be vesicular, resembling chicken pox but lacking the red areola about the vesicle, or morbilliform, resembling measles, but lacking the coryza, cough, and Koplik spots. Occasionally the rash is scarlatiniform. Here, differential diagnosis is almost impossible, since the patient has a red throat, temperature, headache, and vomiting, symptoms common to both poliomyelitis and scarlet fever. The Schultz-Charlton test is always negative, but this, however, does not rule out scarlet fever. The onset of paralysis or paresis establishes the diagnosis of poliomyelitis.

4. *Angiospasm in the skin*: The Schiek test on a paralyzed upper extremity may manifest itself within twelve to twenty-four hours in the form of intense redness with vesiculation. The vesicles may be either confluent or discrete. Occasionally a single large bulla appears. This bulla may rupture and leave a sloughing base. Healing is very slow and takes as long as two to three months. This indolence may be the result of angiospasm, which condition diminishes the blood supply to the tested area and hence fails to remove the toxin causing the sloughing area.

#### PRESUMPTIVE EVIDENCE THAT SYMPATHETIC NERVOUS SYSTEM INVOLVEMENT MAY PRODUCE ANGIOSPASM

A.—Medicine has long accepted the thesis that the cyanosis, muscle spasm, and pain of Raynaud's disease, and the cyanosis and cramplike pain in intermittent peripheral arterial claudication are due to angiospasm.

B.—The chronic poliomyelitic extremity with its cyanosis and muscle spasm and tenderness behaves and responds like the extremity of Raynaud's disease.

C.—External application of heat, in all probability, produces vasodilatation both in the chronic poliomyelitic extremity and in the extremity of Raynaud's disease. The improved circulation to the limbs may be responsible for the improved color, feeling of warmth, and diminution of pain and muscle spasm.

D.—The same results were obtained by White and Smithwick<sup>4</sup> by denervating the spastic blood vessels of the lower extremities of five cases of old poliomyelitis by preganglionic sympathectomy. The blood circulation returned to the extremities. These patients were followed for one year, and the results were reported as very good.

From 1937 to 1947 inclusive, 1,172 acute poliomyelitis patients were admitted to the Kingston Avenue Hospital. Approximately 90 per cent showed evidence of pain and muscle spasm in varying degrees. Six hundred seven, or 51 per cent, developed evidence of anterior horn lesions. Of these, fifty-one died, or 4.25 per cent. Five hundred fifty-six, or 47.5 per cent, were transferred to orthopedic hospitals. Five hundred sixty-five, or 48.25 per cent, were discharged free of neurological symptoms after one- to three-weeks' stay in the hospital.

Since 51 per cent of the acute poliomyelitis patients develop anterior horn lesions or muscle paralysis, and 90 per cent show evidence of pain and muscle spasm, it follows that the sympathetic nervous system may be more responsive to irritation as compared to the central nervous system, hence expressing itself more often, even in the mildest infections. The manner in which it appears to express itself is angiospasm causing ischemia resulting in muscle tenderness and spasm.

#### CONCLUSIVE EVIDENCE THAT ANGIOSPASM EXISTS IN THE ACUTE STAGE OF POLIOMYELITIS

The neuropathology of the spinal cord in poliomyelitis suggests that an inflammation of the anterior horn cells automatically involves the lateral horn in which the sympathetic nerves have their origin. It is reasonable to assume that the lateral horn pathology may be either mild, moderate, or severe. The mildest form expresses itself in ordinary edema. Ivan Wickman<sup>5</sup> states that the edema is of no slight importance from the clinical point of view as it affords a plausible explanation for the rapid disappearance of the neurological signs. Therefore, as soon as the edema subsides in the lateral horn, the angiospasm is released and muscle tenderness and spasm disappear. This is what happens in the patient who recovers in one to three weeks. When the lateral horn is severely damaged the resulting angiospasm may be permanent. The affected extremity may become cold, clammy, and cyanotic.

David Bodian and Howard A. Howe<sup>6</sup> studied the route of transmission of the virus from the portal of entry to the central nervous system. They state that the evidence indicates that the virus migrates peripherally and that the intensity of the lesions of the peripheral ganglia corresponds relatively well to the intensity of the lesions in the adjacent central nervous system. It is of great interest that Sabin and Ward<sup>7</sup> were able to demonstrate virus in the abdominal sympathetic plexus of one case of poliomyelitis, thus indicating at least one pathway of centripetal virus propagation.

We have repeatedly noted lateral and posterior horn involvement in addition to lesions in the intermediate zone similar to those described by Peters.<sup>8</sup> In a few cases we secured portions of the cervical sympathetic chains for histologic examination. It was no surprise to us that we found edema of the ganglia to be present in addition to small foci of infiltration of the ground substance. Very striking in some cases were the degenerative changes in many ganglion cells. Ganglion cells appeared shrunken and nuclei were obscured or absent. In some, coarse basophilic granules were seen in the cyto-

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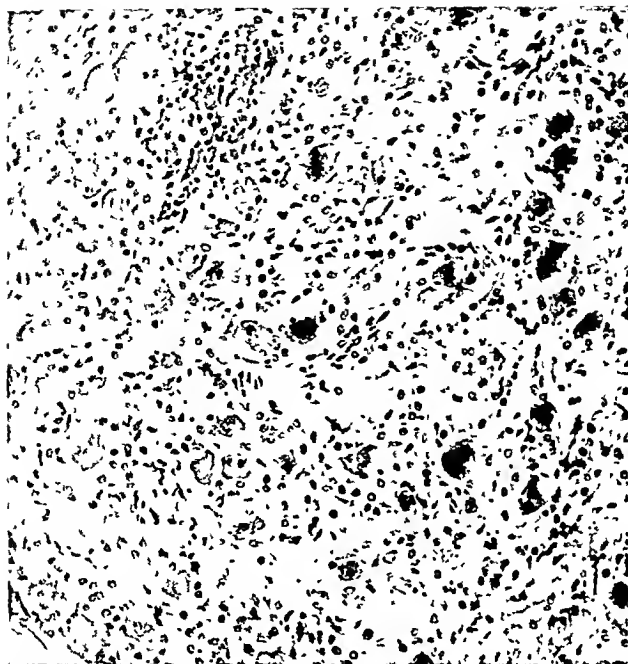


Fig. 1.—Section of sympathetic ganglion in a case of bulbar poliomyelitis, showing round cell infiltration of stroma. (Hematoxylin and eosin stain,  $\times 200$ .)

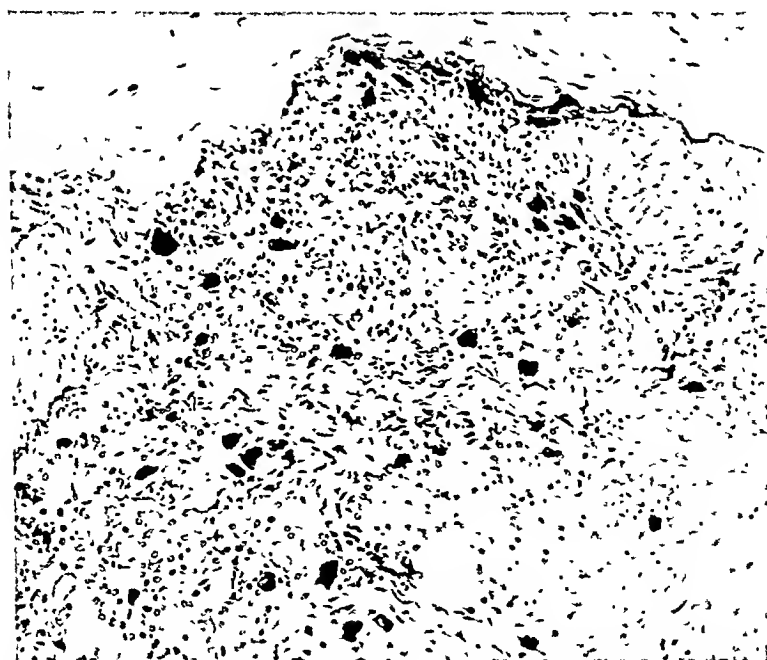


Fig. 2.—Section of sympathetic ganglion in a case of bulbar poliomyelitis showing degenerative changes in ganglion cells. Nissl preparation. (Hematoxylin and eosin stain,  $\times 200$ .)

plasm; nuclear-cytoplasmic distinction was nuclear in some cells, and in others the nucleoli appeared fragmented. Distinct neuronophagia in the sympathetic ganglia was not seen, leading us to the belief that the changes were probably reversible. From our anatomic observations, it was not difficult to explain the functional insufficiency of the sympathetic nervous system as manifested in the clinical observations noted. Steindler<sup>9</sup> has described similar changes.

In 1947 Collens, Foster, and West<sup>10</sup> reported fifteen convalescing poliomyelitis patients treated with paravertebral sympathetic block. Oscillometric recordings were made at the ankles only. Readings made prior to injection gave an average excursion of 1.5. Post block recordings in all patients were increased. Pain, muscle spasm, and tenderness were completely relieved in three patients. All others benefited greatly.

While clinical and therapeutic findings established that angiospasm did exist in the chronic paralytic extremity of poliomyelitis, evidence had to be found to show that a similar condition was present during the acute stage. The oscillometer, therefore, was used to test vascular expansion in all extremities, both paralyzed and nonparalyzed, in acute anterior poliomyelitis. Since emotional disturbances and undue body activity distort the oscillometric readings, and complete cooperation was necessary for accurate findings, we chose twelve patients, mostly adolescent and older, for this study.

*Chart Illustrating Oscillometer Readings.*—Six of the twelve patients studied had one or more extremities paralyzed. The oscillometric excursions were well below the average normal, not only in the paralyzed extremities but in the nonparalyzed as well.

One patient had weakness of back muscles but no evidence of paralysis in the extremities. The oscillometric excursions revealed that the blood vessels in the extremities were in spasm.

Another patient had back muscle spasm and no detectable evidence of paralysis in the extremities. The oscillometric excursions indicated angiospasm in the extremities.

Three patients had no evidence of paralysis on admission and none during the stay in the hospital. The only neurological findings were muscle tenderness and spasm. The oscillometric excursions on the extremities were well below the average normal, thus showing that the blood vessels were not expanding.

The last patient in this study revealed a left facial paralysis and hence polioencephalitis was diagnosed. There was no evidence of any other paralysis anywhere in the body. We decided, on general principles, to test the vascular expansion in the lower extremities and, to our surprise, we found the blood vessels in spasm.

In the lower extremities where the oscillometric readings were very low the dorsalis pedis as well as the anterior tibial pulse was very weak or hardly obtainable. We did not correlate the degree of vasospasm with the degree of muscle spasm or the intensity of the pain. It would appear, however, that the greater the spasm in the blood vessels the more marked the ischemia in the muscles and the more severe the muscle spasm and hence the pain.

TABLE I

OSCILLOMETRIC READINGS																							
AVERAGE NORMAL EXCURSIONS																							
				THIGHS			BELOW KNEES			ABOVE ANKLES			ARMS			FOREARMS							
		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.					
7	7	6	6	4	4	7	7	7	7	7	7	7	7	7	7	7	7	7	7				
ACTUAL EXCURSIONS																							
				THIGHS			BELOW KNEES			ABOVE ANKLES			ARMS			FOREARMS							
		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.		RT.   LT.					
1	21	F	1 1/2	1 1/2	4	2	1 1/2	1 1/2	1 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2	2 1/2				
2	18	M	1	1 1/2	2	3	2	2	1 1/2	4 1/2	4 1/2	4 1/2	4 1/2	4 1/2	4 1/2	4 1/2	4 1/2	4 1/2	4 1/2				
3	15	M	5	3	3 1/2	3 1/2	3 1/2	2	1 1/2	4	4	4	4	4	4	4	4	4	4				
4	18	M	1 1/2	1 1/4	4	4	3	2	1 1/2	3	3	3	3	3	3	3	3	3	3				
5	9	F	1 1/2	1	2 1/2	1	2	2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2				
6	7	F	0	0	1/2	1/4	1/2	1/2	1/4	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2	1/2				
7	11	M	2	1	1	2	1	1	1 1/4	2	2	1 1/4	2	2	2	2	2	2	2				
8	13	M	2	2 1/2	2 1/2	3	1 1/2	1 1/2	1 1/2	3	3	3	3	3	3	3	3	3	3				
9	13	F	1/2	1 1/4	1 1/2	1 1/2	1	1	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2	1 1/2				
10	11	M	2	2 1/2	2 1/2	2 1/2	2	2	1 1/2	2	2	2	2	2	2	2	2	2	2				
11	6	M	2	2	1 1/4	2	1	1	1	3	3	3	3	3	3	3	3	3	3				
12	8	M	2 1/2	2 1/2	5 1/2	3 1/2	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4	1 1/4				
				OTHER																			
				EXTREMITIES				OTHER															
				RU.		RL.		LU.		LD.		OTHER											
1	21	F	P.P.*	x†	x	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
2	18	M	P.P.	x	x	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
3	15	M	P.P.	x	x	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
4	18	M	P.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
5	9	F	P.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
6	7	F	P.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
7	11	M	P.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
8	13	M	P.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
9	13	F	N.P.†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
10	11	M	N.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
11	6	M	N.P.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
12	8	M	Polio. Enceph.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				

\*P.P., Paralytic poliomyelitis.

†N.P., Nonparalytic poliomyelitis.

‡X, Paralysis.

§0, No paralysis.

## METHODS FOR RELIEF OF PAIN AND SPASM

Having convinced ourselves that the blood vessels were in spasm in the acute stage of poliomyelitis and that the ischemia might be responsible for the muscle pain and spasm, we set out to relieve the angiospasm by mechanical means.

Since hot packs were introduced for the relief of muscle spasm and pain, we have steadily looked for a more pleasant and less laborious method to replace it. Short wave diathermy produces clean, comfortable, controlled heat which is easily tolerated. We introduced it to an extremity showing angio- as well as muscle spasm with pain. After treating the extremity for a short period of time the muscle relaxed and the pain diminished or subsided. To bring more blood to a spastic muscle, a rhythmic constrictor was introduced to assist the dilated blood vessels in supplying blood to the ischemic muscle. Quicker and better results were obtained. The muscles relaxed and the pain diminished or subsided, only to return when the artery or arteriole went back into spasm.

Both hot packs and short wave diathermy produce vasodilatation with relief of muscle pain and spasm. Both methods require trained personnel and are very expensive.

We therefore decided to use vasodilator drugs by mouth. We chose nicotinic acid as the vasodilator and gave it in doses of 100 mg. This drug dilated the nonspastic blood vessels and showed no effect on the spastic blood vessels. The patient would either become flushed or state that he felt warm in the non-paralytic areas and cold in the paralytic areas; thus showing that the drug would not dilate the spastic blood vessels.

At this time our patients were transferred to orthopedic hospitals and our experiment terminated. At the same time Graubard, Robertazzi, and Peterson<sup>11</sup> reported 140 patients treated with intravenous procaine. They classified their cases (1) traumatic, (2) inflammatory, and (3) miscellaneous.

"In the miscellaneous cases we found some interesting phenomena. We did not expect to find any changes in the neurologic cases, but treated them in order to see if any improvement could be noted. In two cases of anterior poliomyelitis, with flaccid paralysis of many years' duration, there was the following response: during the infusion the patients stated that a tingling sensation of warmth crept down the affected extremities. This vaso-dilatation was maintained following each injection for several days and even weeks. This prompted us to try procaine infusions in two cases of spastic anterior poliomyelitis. The results were relief of spasm, increased mobility and improved muscular control. From our observations, the use of intravenous procaine in alleviating muscle spasm suggests its therapeutic application in the symptom relief of the distress of acute anterior poliomyelitis.<sup>12</sup> The use of curare in conjunction with physical therapy has given some very satisfactory improvement. The use of procaine intravenously in patients who have been on curare therapy every eight hours for one month with only slight improvement and relaxation of the spasticity, responded with what might be termed a dramatic response."

## SUMMARY

We have presented clinical evidence showing that sympathetic nervous system involvement in acute poliomyelitis may manifest itself in the cervical region by Horner's Syndrome, in the thoracic region by spasm of the pulmonary blood vessels with dilatation and irregularity of the right side of the heart, in the gastric region by pylorospasm, in the intestinal region by constipation or diarrhea, in the rectal region by intestinal obstruction, in the bladder region by retention or incontinence of urine and in the skin by angio-paresis or spasm.

Presumptive evidence has been presented to show that the blood vessels in the chronic poliomyelitic extremity behave and respond similar to the angio-spasm of Raynaud's disease or the cramplike pain in intermittent peripheral arterial claudication.

Conclusive evidence that the blood vessels were in spasm was found in the twelve patients tested with the oscillometer. The actual excursions were far below the normal. We have also shown that angiospasm was present in the encephalitic, paralytic, and in the nonparalytic extremity of acute poliomyelitis. Pathologic evidence to substantiate the clinical findings was presented by showing involvement of the lateral horn as well as of the sympathetic ganglia.

We have demonstrated that short wave diathermy with the rhythmic constrictor dilated the blood vessels and increased the blood supply to the extremity. The muscles relaxed and the pain diminished or subsided only to return when the blood vessels contracted.

However, we feel that neither short wave diathermy nor hot packs are the solution for the relief of the muscle spasm and pain in acute poliomyelitis, since these methods do not produce sustained vasodilatation. The method of choice would be a drug that could be administered by mouth, subcutaneously, or by the intravenous route.

We fully understand that the subject matter in this paper is debatable. We hope, however, that it will provoke others to investigate further the role of the sympathetic nervous system in acute poliomyelitis, and that it will eventually lead to a better understanding of the clinical picture of the disease and hence to a more scientific therapeutic approach.

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## HISTOPLASMOSIS IN CALIFORNIA CHILDREN

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CURRENT textbooks<sup>1-3</sup> describe histoplasmosis as a highly fatal disease rarely diagnosed before autopsy. The invading organism, *Histoplasma capsulatum*, is a fungus which in the tissues resembles protozoal bodies and produces a clinical picture somewhat similar to kala-azar.

A severe infection is characterized by irregular fever, anemia, leucopenia, emaciation, and cough. There may be enlargement of the lymph nodes, spleen, and liver, and ulcerations in the gastrointestinal tract.

The fungus apparently usually enters through the mouth but also has been described as entering through a cutaneous ulcer. Autopsy findings most frequently describe enlargement of mesenteric lymph nodes and extensive ulceration of the intestinal mucosa. Pulmonary invasion described in the fatal cases was thought to be part of the generalized disease and not the primary infection.

### SOURCE OF INFECTION

*Histoplasma capsulatum* survives the action of gastric juice in experimental infection of dogs.<sup>4</sup>

The organism has not been found in nature but has been isolated from dogs, which raises the question of domestic pets as carriers.

### INCIDENCE (AGE AND SEX)

Histoplasmosis has been described as occurring at any age from three months to seventy years with 28 per cent below age 13 years.<sup>1-3</sup> Among adults there were three times as many male as female patients with less disproportion among children (one and one-half times as many cases in boys as girls).

The U. S. Army reported cases among whites, Negroes, Japanese, Chinese, and Filipinos.<sup>1</sup> No occupation studies have appeared.

### SYMPTOMS

The first studies in 1906 by Darling<sup>5</sup> described histoplasmosis as a chronic disease characterized by fever, emaciation, anemia, leucopenia, and splenomegaly with a duration of three weeks to eight months. Later studies recognized other aspects such as involvement of skin and mucous membranes especially about the nose and mouth.

In children there is an insidious onset with loss of weight, fever, gastrointestinal disturbances, and coughing. The liver, spleen, and lymph nodes show enlargement. Mesenteric lymphadenitis and enlargement of the hilar lymph nodes are almost always reported at autopsy. The supposition is that these follow ulceration of the bowel and dissemination to the lungs. (Involvement of the bone marrow sometimes produces anemia and leucopenia.) Lymphocytosis is usually found in children.

Lesions in the lung are composed of multiple small foci widely distributed. They may be pleural or subpleural and often cause pleurisy-like pain. There may be râles in the bases but otherwise physical examination of the chest is negative.

#### X-RAY FINDINGS

The usual picture shows enlargement of hilar lymph nodes, peribronchial thickening, and multiple miliary calcifications.<sup>6</sup>

These residual calcifications after infection with histoplasmosis have not been shown to have any clinical significance. The same is true of coccidiomycosis which is caused by a related organism.

#### MYCOLOGY

The organism belongs to the fungus family of Endomycetes which is the chief mold group identified as causing disease in man.<sup>7</sup>

Another fungus in this same family classification is *Coccidioides immitis*.

*Histoplasma capsulatum* is primarily a parasite of the reticuloendothelial system<sup>8</sup> and is demonstrated in the macrophages. Extracellular forms have rarely been found and in this respect it differs from all other pathogenic fungi.

The fungus when demonstrated in peripheral blood or from a biopsied lymph node appears as small oval bodies within the large mononuclear cells. An oval body measures 1 to 5 microns and has a thick capsule. On culture media this yeastlike form buds and mycelia grow. The fungus produces distinctive chlamydospores which are smooth, thick-walled, and tuberculated.

From 1906 to 1937 only thirteen cases were reported in the literature. Many more have been reported since then.

Within the last two years studies have shown that histoplasmosis is not necessarily a fatal disease but that it is apparently benign or even subclinical in many aspects.

Christie and Peterson<sup>9</sup> at Vanderbilt University reviewed the problem of calcification occurring in the chests of children who were not sensitive to tuberculin.

From many sections of the United States there was reported a high incidence of pulmonary calcification in young people who had repeatedly negative tuberculin skin tests.

For example, Gass and his associates<sup>10</sup> studied 1,167 school children in Tennessee with serial x-rays and skin tests over a four-year period. They found 83 per cent of white children and 72 per cent of Negro children had pulmonary calcifications and negative tuberculin tests. This was a local phenomenon.

Other studies showed the incidence of pulmonary calcification was forty times as high in Tennessee as in Alabama.<sup>6</sup> Since calcified lesions in the chest had always been considered tuberculosis in the past, the specificity of the tuberculin skin test was sharply questioned.

After Dr. Charles E. Smith<sup>11</sup> of Stanford had demonstrated that coccidioidomycosis produces a primary complex which goes on to calcification indistinguishable from that of tuberculosis, Christie and Peterson did routine skin testing of children in Tennessee with coccidioidin and histoplasmin. They



found a very high correlation between pulmonary calcification and positive histoplasmin reactions. *Coccidioides* was not a factor in their study.

Large-scale skin-testing programs were carried out in other geographical areas, i.e., Ohio, Kansas, and Michigan, where pulmonary calcifications were found in tuberculin negative persons.<sup>12, 13</sup>

The conclusions were reached that (1) a mild or even subclinical form of histoplasmosis was responsible for a high proportion of calcifications seen in x-rays of tuberculin negative reactors; (2) the greatest prevalence of this phenomenon was found in the area of the eastern slope of Mississippi River Basin. Supporting these conclusions, a geographical pattern of cases of disseminated military calcifications emerged from the Selective Service induction x-rays. These showed the highest incidence to be among men from the lower Mississippi River Basin.

#### SKIN TESTING

The preparation used in skin testing is histoplasmin 1:100 dilution, 0.1 c.c. applied intradermally. Tests are read in seventy-two hours. This time is selected because skin-test sensitivity to histoplasmin is reported to rise sharply at forty to sixty hours and to remain present for two to three weeks. A positive reaction consists of edema surrounded by a large area of erythema. The diameter of the area of induration must be 5 mm. or over to be considered a positive test. Slight desquamation usually follows. There is neither induration or erythema in a negative test.

The significance of a positive histoplasmin test is like the tuberculin test in being a satisfactory exclusion test in subacute and chronic forms of the infection.

The specificity of the test is not as good in experimental animals as in man, but continued studies indicate that reactions observed are truly allergic phenomena related to antecedent infection. There is some cross sensitivity with blastomycin.<sup>14, 15</sup>

Special tuberculin luers and needles should be used for all testing to avoid adsorption on syringes.

Following Dr. Christie's reports of mild and subacute cases of histoplasmosis in children in the South, it seems reasonable to suppose that mild infections with this fungus may occur in other sections of the country.

With this possibility in mind the author skin-tested a series of eighty-five children in California who had suggestive clinical symptoms. In every case the histoplasmosis-testing was done with material supplied by Dr. Christie and followed the technique described above.

For the tuberculin testing P.P.D. was used, 0.1 c.c. intradermal of No. 1 followed by 0.1 c.c. of No. 2. Brief case reports of children with positive histoplasmin and negative tuberculin skin tests are presented.

#### CASE REPORTS

CASE 1.—Jimmy aged 6½ years.

*Past History.*—The child was born in Boston but lived for two years in Texas and Arizona. He had scarlet fever at the age of 3 years followed by recurrent bronchitis. For the past two years he has coughed at night.

*Presenting Complaints.*—Great fatigue, loss of weight, nightmares, evening temperature 100-101° F., and night cough.

*Physical Examination.*—A pale, listless child who was eight pounds underweight for his body build. Positive findings included anterior and posterior cervical lymphadenitis, posterior pharynx granular, and occasional râles in the chest.

*Laboratory Findings.*—Red blood cells 3.6 million to 3.9 million, hemoglobin 10.15 to 11.95 Gm., white blood cells 7,100 to 12,000, polymorphonuclears 36 to 42 per cent, lymphocytes 62 to 54 per cent, eosinophiles 3 to 6 per cent, sedimentation rate 30 to 11 mm. fall per hour, stomach washing negative for tubercle bacillus.

*Skin Tests.*—Tuberculin, three negative reactions in ten months. Coccidioidin negative. Histoplasmin violently positive, area of erythema 5 x 6 cm. with indurated center at seventy-two hours, followed later by mild desquamation.

*X-ray Chest.*—Shows multiple miliary calcifications in the parenchyma (see Fig. 1).



Fig. 1.

CASE 2.—Bruce aged 5½ years.

*Past History.*—This child was born in California and went to Texas for two years while his father was stationed there in military service. Soon afterward when the family returned to California the boy started to cough and this continued for eight months.

*Presenting Complaints.*—Chronic cough, worse at night; loss of weight and failure to gain; irritability; apprehension, fatigue, and occasional bouts of elevated temperature.

*Physical Examination.*—A hypertonic, overactive boy who was five pounds underweight for his body measurements. Tonsils were moderately hypertrophied and pitted; cervical lymph nodes were palpable and no râles were heard in his chest.

*Laboratory Findings.*—Blood count and sedimentation rate were within normal limits.

*Skin Tests.*—Tuberculin negative. Coccidioidin negative. Histoplasmin positive.

*X-ray Chest.*—Shows multiple hilus gland enlargements and multiple discrete calcium deposits far out in the parenchyma both sides (see Fig. 2).

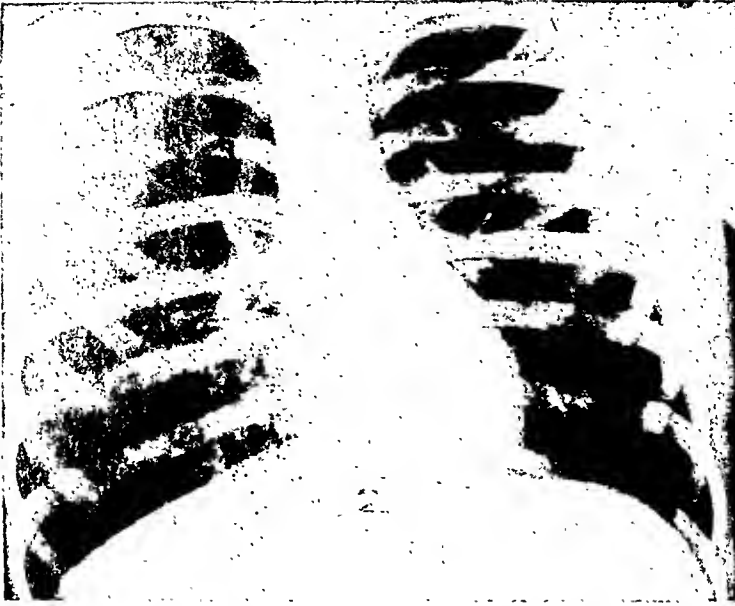


Fig. 2.



Fig. 3.

CASE 3.—Walter aged 7 years.

*Past History.*—The boy was born in San Francisco and has lived near there all his life except for one visit to Missouri of one month duration. He has had recurrent attacks of asthma and is sensitive to a number of pollens and epidermals.

*Presenting Complaints.*—Sharp, stabbing precordial pain produced by deep breathing, fatigue with great languor, and afternoon temperature of 100-100.8° F.

*Physical Examination.*—Pale, slow-moving boy with satisfactory nutritional status. Tonsils hypertrophied and eryptic, cervical glands enlarged and tender. Shallow breathing but no frietion rub noted. Rather diffuse tenderness over right lower quadrant to deep palpation.

*Laboratory Findings.*—Red blood cells 4.2 million, hemoglobin 12.85 Gm., white blood cells 6,050, polymorphonuclears 23 per cent, lymphocytes 55 per cent, eosinophiles 16 per cent, monocytes 6 per cent; sedimentation rate 22 mm. fall per hour. Electrocardiogram normal for age.

*Skin Tests.*—Tubereulin negative. Histoplasmin positive, 3 × 3 cm. followed by desquamation.

*X-ray Chest.*—Shows multiple miliary calcifications with several lymphatic courses back to the hilus nodes (see Fig. 3).



Fig. 4.

CASE 4.—Barbara aged 11 years.

*Past History.*—This child has lived most of her life in Wyoming and came to California two years ago.

*Presenting Complaints.*—Nonproductive cough and draining ear for duration of four months, recurrent attacks of asthma and urticaria, evening temperature.

*Physical Examination.*—Emaciated-looking girl with very droopy posture who was twelve pounds underweight for her body build. She had posterior cervical lymphadenitis, a sour smelling discharge from her left ear, a few high pitched asthmatic râles in both lung bases, and moderate tenderness over her right lower quadrant on palpation of the abdomen.

*Laboratory Findings.*—Red blood cells 4.1 million, hemoglobin 11.82 Gm., sedimentation rate 12 mm. fall per hour. Aspergillus feund in smear from ear.

*Skin Tests.*—Tubereulin negative. Histoplasmin positive, 2 × 3 cm. with induration.

*X-ray Chest.*—Shows enlarged hilus glands and several small calcifications especially on the right side (see Fig. 4).

CASE 5.—Sally aged 9½ years.

*Past History.*—This girl, born near San Francisco, has never been away from home farther than one hundred miles. She has had pneumonia twice and recurrent attacks of asthma. In infancy she was allergic to wheat, eggs, and milk.

*Presenting Complaints.*—Intermittent fever usually in the evening, dry cough, worse at night, duration 18 months; headaches, pyelitis, and loss of weight.

*Physical Examination.*—Droopy, emaciated-looking girl who is thirteen pounds underweight for her build. Cervical lymph glands were hard, shotty, and not tender. The mucous membranes of her nose and throat were pale and she had a few fine moist râles in her chest. Lymph nodes in her right groin were palpable and so was her spleen.

*Laboratory Findings.*—Red blood cells 3.95 million, hemoglobin 10.95 Gm., white blood cells 7,300, polymorphonuclears 36 per cent, lymphocytes 51 per cent, eosinophiles 12 per cent, monocytes 1 per cent, sedimentation rate 17.9 mm. fall per hour.



Fig. 5.

*Skin Tests.*—Tuberculin negative. Histoplasmin positive. Coccidioidin negative.

*X-ray Chest.*—Shows rather massive hilar enlargement on both sides with multiple discrete pulmonary calcifications in the parenchyma. There are many lymphatic courses back to the hilar nodes (see Fig. 5).

#### SUMMARY

A review of the current status of histoplasmosis is presented.

The probability of wide-spread infection of a mild or subclinical form of histoplasmosis is pointed out.

Case histories are summarized on five children with multiple pulmonary calcifications all of whom are tuberculin-negative and histoplasmin-positive to intradermal skin tests.

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## CUSHING'S SYNDROME IN CHILDREN

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### INTRODUCTION

IN 1932 Harvey Cushing<sup>1</sup> separated from a welter of case reports on polyglandular dyscrasias a group of patients with a common clinical picture. This syndrome, which is now associated with his name, was thought by Cushing to be a manifestation of hyperactivity of a basophilic adenoma of the pituitary gland. He suggested the term basophilism. In the light of subsequent investigations his original thesis as to pathogenesis has not been substantiated; nevertheless, the syndrome he described has been generally accepted as a clinical entity.

Albright<sup>2</sup> has summarized the cardinal clinical features of Cushing's syndrome as follows:

(a) Diabetes which is usually mild and often only demonstrable as an unresponsiveness to an alimentary hyperglycemia (i.e., decreased sugar tolerance), but which is resistant to insulin.

(b) Muscular weakness with a low creatinine as indicative of decreased muscular mass.

(c) Osteoporosis, especially of the spine (not to be confused with osteitis fibrosa generalisata or with osteomalacia, since the serum phosphatase level is normal rather than high), associated with hypercalcinuria early in the disease, and, in many instances, with nephrolithiasis.

(d) A thin, reddish (?transparent) skin, easy bruisability, often large purplish striae, and a marked susceptibility to skin infections.

(e) Impotence in men and amenorrhea in women.

(f) Mild to moderate obesity with a tendency for the fat to be deposited in the neck and face ("moon-face") and to spare the extremities.

(g) Mild hirsutism without other evidence of virilism (clitoris not enlarged, thyroid cartilage and voice normal in female patients) usually but not always associated with a slight to moderate elevation in the urinary excretion of the 17-ketosteroids.

(h) Mild erythrocytosis (red count circa 5.8 million) without increased blood volume.

(i) Hypertension and arteriosclerosis, often accompanied by coronary disease and vascular disease of the kidneys.

### LITERATURE

Prior to and subsequent to Cushing's article describing the symptom complex and postulating its relationship to hyperactivity of the basophilic cells of the pituitary, sporadic case reports appeared describing a similar syndrome in

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association with hyperplasia or a neoplasm of the adrenal cortex. Cushing was well aware of the frequent occurrence of histologic evidence of overactivity of an adrenal cortex, but felt that the adrenal changes could be explained on the basis of pituitary stimulation, as there were other examples of changes in distant tissues initiated by the pituitary.

Crooke,<sup>3</sup> in 1935, made a fundamental observation in respect to the pathology of basophilism or Cushing's syndrome. He demonstrated characteristic hyaline changes or peculiar areas of degranulation in the basophile cells of the pituitaries in twelve patients with typical clinical pictures. As a rare chance finding this change was found to a minor degree in nine out of 350 control pituitary glands. In those control patients in which the change was found, it was not associated with any particular disease or symptom complex. In this communication Crooke brought out the following additional features in respect to the pathology of the condition:

(a) A basophile adenoma was not an essential feature; and in those cases where such an adenoma was present, in none of the cells constituting the adenoma was the hyaline change found, although it was present in basophile cells throughout the remainder of the gland.

(b) Adrenal cortical hyperplasia or neoplasia was a frequent but not constant finding.

(c) In three of Crooke's twelve patients there was a neoplasm of the thymus. This complication has not been reported by other authors.

Crooke's findings in the pituitary have been amply confirmed by Eisenhardt and Thompson.<sup>4, 5</sup> The hyaline changes in the basophiles of the pituitary may be considered beyond reasonable doubt as the one constant pathologic finding in basophilism, and one may say that, where verification by histologic examination of the pituitary is possible, it is the *sine qua non* in the definitive diagnosis of Cushing's syndrome.\* This statement does not imply that pituitary malfunction is necessarily the primary or initiating factor. There has been much discussion in the literature concerning the pathogenesis of this condition and the manner in which the protean physiologic aberrations and pathologic changes are mediated. These matters will be more fully considered under discussion.

Relatively few examples of Cushing's syndrome in individuals prior to puberty have been reported. Even fewer are those cases in which there has been a complete post-mortem study.

Marks, Thomas, and Warkany (1940)<sup>7</sup> discuss adrenocortical obesity in children in relation to twenty-three cases they collected from the literature and one case of their own. Some of the cases they described apparently would have fulfilled the requirements of Cushing's syndrome, others seemed to bear a more intimate relationship to the adrenogenital syndrome with virilism, and still others appeared to be of a mixed type or a combination of these two conditions. The authors recognized the close similarity of the findings in some cases of

\*However, to practically every generalization there is always an exception. Kepler<sup>6</sup> quotes a case of Reforzo-Membrives & del Castillo of Buenos Aires which had been brought to his attention. The patient was typical clinically but at necropsy all the endocrine glands were grossly and microscopically normal. Sections of the pituitary showed no evidence of Crooke's changes.



adrenocortical obesity and Cushing's syndrome but apparently dismissed the possibility that in at least some of these cases they might be dealing with a preadolescent type of basophilism because pituitary adenomata occurring in children associated with Cushing's syndrome had not been described. This concept is untenable for two reasons: first, it has been repeatedly demonstrated that a basophile adenoma of the pituitary is not a constant finding in basophilism; and second, although rare, basophile pituitary adenomata in children associated with basophilism have been reported.<sup>8-13</sup> One of the authors, Warkany (1945),<sup>14</sup> however, has apparently subsequently modified his views because in the section on hyperadrenocorticism, of which he is the contributor, in Mitchell and Nelson's *Textbook of Pediatrics*, one of the subsections is entitled "Cushing's syndrome of Adrenocortical Obesity." In only one of the cases (i.e., that of Crooke and Callow<sup>15</sup>) cited by Marks, Thomas, and Warkany, were Crooke's changes of the pituitary described. In the protocols of most cases collected by these authors it is not possible to determine what staining techniques were employed to study the pituitary. It is possible that hyaline changes in the basophiles would have been more frequently encountered if suitable staining techniques had been employed. With routine hematoxylin and eosin preparations the characteristic hyaline changes are practically impossible to discern. However, if present, they are beautifully displayed as hyaline areas of degranulation if suitable special stains are employed, such as advocated by Crooke and Russell.<sup>16</sup>

Farber, Gustina, and Postoloff<sup>17</sup> in 1943 reviewed the cases of Cushing's syndrome in children which had been reported up to that date and added a case of their own, making a total of twenty-seven cases. In view of the close similarity of the symptom complex attributed to basophilism and that of adrenocortical obesity, it is remarkable that only one case (Crooke and Callow<sup>15</sup>) was common to the series of Cushing's syndrome collected by these authors and that compiled by Marks and associates<sup>7</sup> concerning adrenocortical obesity.

Farber and his associates did not include in their series the two cases described by Gross (1940)<sup>18</sup> (Cases 4 and 5) of carcinoma of the adrenal cortex with a syndrome similar to pituitary basophilism. Although both of these patients had some of the characteristics of Cushing's syndrome, neither had all the cardinal features. The pituitary in Case 4 was reported microscopically to have a cyst of the pars intermedia which compressed the pars anterior. The pituitary in Case 5 was judged microscopically to be normal. In neither case was mention made of Crooke's changes in the basophiles of the pituitary.

Albright (1943)<sup>2</sup> described a case of Cushing's syndrome in a girl 12 years of age. Extensive metabolic studies have been carried out on this patient. Dr. Albright<sup>19</sup> has informed us this patient is still living.

Heinbecker (1944)<sup>13</sup> reported two cases of Cushing's syndrome in children, one (Case 3, his series) in a boy 12 years of age. This appears to be a typical case of basophilism. At post-mortem examination there was atrophy of the right adrenal and hypertrophy of the left. The pituitary showed a basophile adenoma and partial hyalinization of the basophiles. He also described

atrophy of the nuclear cells of the hypothalamic and preoptic areas, particularly in the paraventricular nuclei. The author believes these changes to be of special etiological significance in respect to basophilism. His second patient (Case 5) does not appear to have a pure Cushing's syndrome but rather a mixed case of basophilism and adrenogenital syndrome, as there was also evidence of virilism. At operation a right adrenocortical tumor was removed.

Weisse (1947)<sup>20</sup> recorded a case of Cushing's syndrome in a female infant aged 20 months. A tumor of the left adrenal cortex was removed surgically. The infant died on the third postoperative day. A post-mortem examination was performed. The remaining adrenal was not unusual. The pituitary was apparently normal. No specific mention was made in regard to the presence or absence of Crooke's changes. This was also possibly a mixed case as evidence of virilism was present in the form of an enlarged clitoris.

Allibone, Baar, and Cant<sup>21</sup> reported two patients with adrenocortical obesity or Cushing's syndrome associated with adrenal cortical carcinomas. Both patients showed an extreme obesity and mild hirsutism but in neither was there masculinization or precocious growth. In one, apparently the pituitary was not examined; in the other, Crooke's changes were present in the basophiles.

Excluding the series of cases of adrenocortical obesity reported by Marks and his associates<sup>7</sup> the total to date of reported cases of Cushing's syndrome in children is as follows: Of the twenty-seven cases collected by Farber and associates,<sup>17</sup> two cases can probably be excluded, i.e., Case 2, reported by Reichmann,<sup>22</sup> because the patient was 36 years old at the time of death and the age of onset of symptoms was indefinite, and Case 3, reported by Teel,<sup>23</sup> because of insufficient clinical data. To the remaining twenty-five cases may be added the following: Gross (two), Albright (one), Heinbecker (one), Weisse (one), Allibone and associates (two), and the authors herein report an additional example of Cushing's syndrome in a child with post-mortem findings, bringing the total to thirty-three.

#### CASE REPORT

*Clinical History.*—S. G. was an 8-year-old white girl whose growth and development were normal until 4½ years of age (Fig. 1). Shortly after this time she began "to put on weight" and seemed "fat in the face." Her family physician judged her to be overweight but otherwise normal. During the ensuing three and one-half years the abdomen became protuberant and excessive weight gain continued. Diet restriction and thyroid extract were employed without success.

One year after the onset of the obesity, stunting of stature became increasingly evident, and in the three years prior to hospitalization there was no appreciable gain in height.

At approximately 7 years of age her mother noted the appearance of pubic hair. There were occasional episodes of back pain and abdominal discomfort. The child also complained of intermittent headaches of moderate severity. No polyphagia, polydipsia or polyuria were noted. She had never menstruated and had the normal, high-pitched voice of a child.

Concomitant with the development of the unusual changes in body contour, her general health was considered to be satisfactory. Progress at school was normal but she was unable to take an active part in playground games with other children because of some exertional dyspnea.



Fig. 1.—Patient S. G. to the right, at age of  $4\frac{1}{2}$  years, with her younger brother.

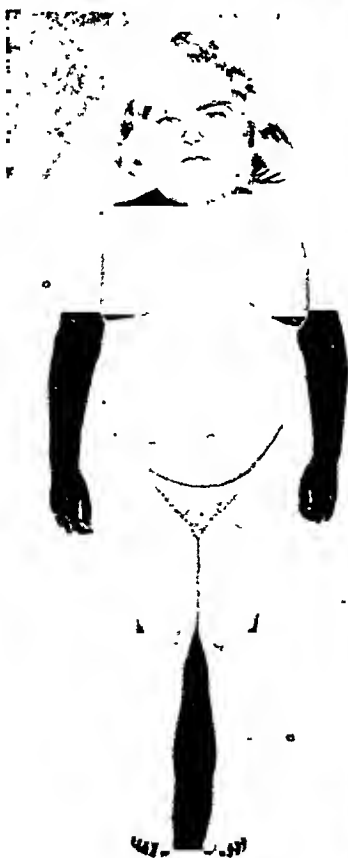


Fig. 2.



Fig. 3.

Figs. 2 and 3.—S. G. at time of admission, 8 years of age.

*Family History.*—The immediate family history was not significant. A distant female cousin of our patient died at 10 years of age with primary atrophy of the adrenal glands.\* The maternal grandmother of this cousin and the maternal grandfather of our patient were brother and sister. Although this is probably coincidental, it seems unusual that even distant cousins should suffer from two rare maladies in which the adrenal cortex is involved.

*Physical Examination.*—This girl was short, 44½ inches (111.25 cm.) and showed the characteristic "buffalo" obesity involving the face and trunk and sparing the extremities (see Figs. 2 and 3). Her weight was 65 pounds (29.5 kilos). Her face was broad and florid with full cheeks and prominent double chin. The chest and shoulders were broad and thick with pendant, widely separated, flabby breasts in which no glandular tissue was felt. The abdomen was protuberant. Over the flanks and upper thighs there were purple striae. There was a prominent fat pad at the base of the neck, the shoulders were rounded, and the spine had lost the normal dorsal and lumbar curves. The extremities were little involved in the obesity and seemed slender in relation to the trunk. On the face, extremities, and back was present an excessive growth of fine, soft, fair hair. Crisp dark hair was present in the axillae and over the pubes, the latter showing the female distribution. Mild acne was noted on the face. The eyes, ears, nose, and throat were negative. The neck was short and thick. There were no enlarged glands. The thyroid was not palpable. The chest was symmetrical with good expansion. The lungs were clear to percussion and auscultation. The heart was not enlarged, sounds clear, normal rate, and rhythm regular. The blood pressure was 148/100. No organs or tumor masses could be palpated through the obese abdominal wall. Although there was an abundant growth of pubic hair, the external genitalia were not unusual. The clitoris was not enlarged. A vaginal examination was not done. The reflexes were physiologic.

*Laboratory Investigations.*—*Urine:* Urine was acid; albumin, 0; sugar, trace, and repeated samples were negative; microscopic examination, sediment showed occasional white blood cells.

*Blood:* Hemoglobin was 16.6 Gm.; red blood cells, 5,100,000; hematocrit, 50 per cent; and white blood cells, 17,600.

*Blood chemistry:* Serum calcium was 5.12 meq. per liter (10.3 mg. per cent). Inorganic serum phosphorus, 1.9 meq. per liter (3.4 mg. per cent). Serum alkaline phosphatase, 20.3 King Armstrong units. Nonprotein nitrogen, 34.8 mg. per cent. Fasting blood sugar, 87.0 mg. per cent. Serum chlorides, 103.1 meq. per liter (598 mg. per cent NaCl). Serum sodium, 140.8 meq. per liter (324 mg. per cent).

Glucose tolerance test using 100 Gm. of glucose: urine, negative each time; blood, at fasting, 79 mg. per cent, at thirty minutes, 121 mg. per cent, at sixty minutes, 154 mg. per cent, at one hundred twenty minutes, 120 mg. per cent, at one hundred eighty minutes, 115 mg. per cent.

Total neutral 17-ketosteroids excretion, 6.2 mg. per twenty-four hours.

Calcium balance test, negative balance with hypercalciuria: calcium intake, 1 Gm. per 24 hours; calcium in urine, 1.3 Gm. per twenty-four hours; calcium in stool, 0.12 Gm. per twenty-four hours.

Nitrogen balance test, positive balance: nitrogen intake, 37.9 Gm. per seventy-two hours; nitrogen excreted in stool in seventy-two hours, 7.16 Gm. Nitrogen excreted in urine in seventy-two hours, 22.5 Gm.

Basal metabolism rate, -12. Corrected for normal weight for height, +3.

Postoperative determinations: serum chloride, 109.2 meq. per liter (634.4 mg. per cent NaCl); serum sodium, 134.8 meq. per liter (310 mg. per 100 c.c.); nonprotein nitrogen, 35.4 mg. per cent.

*X-Ray Examination.*—All the bones visualized showed a generalized osteoporosis. The dorsal and lumbar spine presented an unusual amount of osteoporosis and a lack of the normal dorsal and lumbar curves. Some of the vertebrae, particularly the twelfth dorsal and the first lumbar, showed evidence of compression. The intervertebral spacings were increased in width (Fig. 4).

\*We are indebted to Dr. R. E. Miller of the Department of Pathology and Bacteriology, Dartmouth Medical School, for furnishing us with details of the post-mortem findings on this girl.

*Progress.*—There was no essential change in this child's condition while she was under investigation in the hospital. A clinical diagnosis of Cushing's syndrome was made, probably associated with adrenal hyperplasia or tumor. As it was the consensus of many consultants that untreated her prognosis was poor, it was decided to explore her and remove one adrenal if no tumor was found.



Fig. 4.—Lateral roentgenogram of dorsal and lumbar spine, showing osteoporosis, collapse, and wedging of the vertebral bodies, particularly T12 and L1.

*Operation and Postoperative Course.*—On the night preceding operation, she received 15 c.c. of Adrenal Cortical Extract\* subcutaneously and immediately prior to operation, 15 c.c. intravenously. Codeine and hyosine were used for preoperation sedation. Under ether anesthetic an exploratory operation was performed. No adrenal tumor was present. The left adrenal gland was removed, together with several small yellow to brown-red nodules from the periadrenal fat. This gland was similar in all respects to the right. Both will be described with the post-mortem findings. The child withstood the operation well and seemed bright and comfortable after consciousness had been regained. The postoperative blood pressure was 120/110, the pulse, 120. During the next ten hours the pulse became rapid and irregular. Despite the intravenous administration of a total of 43 c.c. of adrenal cortical extract, the blood pressure fell steadily to 106/86. Quite suddenly, twenty-two hours postoperatively, her

\*Connaught Medical Research Laboratory Adrenal Cortical Extract, biologically standardized to contain 30 units per cubic centimeter, was employed.

pulse and blood pressure became unobtainable and remained so for one hour. The blood pressure then returned to average about 80/65. Following this she became anuric and her serum chlorides (109.2 meq. per liter) began to rise. Serum sodium (134.8 meq. per liter) was slightly below normal and the nonprotein nitrogen was within normal limits. She also complained of pain in the left chest posteriorly and the possibility of a pulmonary embolus or massive collapse was considered. However, this was not confirmed by x-ray.

During the second postoperative day the blood pressure remained about 65/50 although the child continued to seem bright and adjusted her own covers. Despite continued administration of adrenal cortical extract (80 e.c.) the blood pressure again became unobtainable, her temperature rose to 104° F., coma ensued, and she died forty hours postoperatively.

#### AUTOPSY

Gross.—Externally, in addition to the obesity, the body showed the peculiar stigmata of Cushing's syndrome described in the clinical section. The abdominal fat measured 3 cm. in thickness and there were large masses of adipose tissue in the omentum and paravertebral gutters. Fat necrosis was noted in the depths of the recent surgical incision in the left flank. The thymus was atrophied. The heart (weight, 163 grams) showed a moderate degree of left ventricular hypertrophy. The lungs displayed a few small areas of superficial collapse.

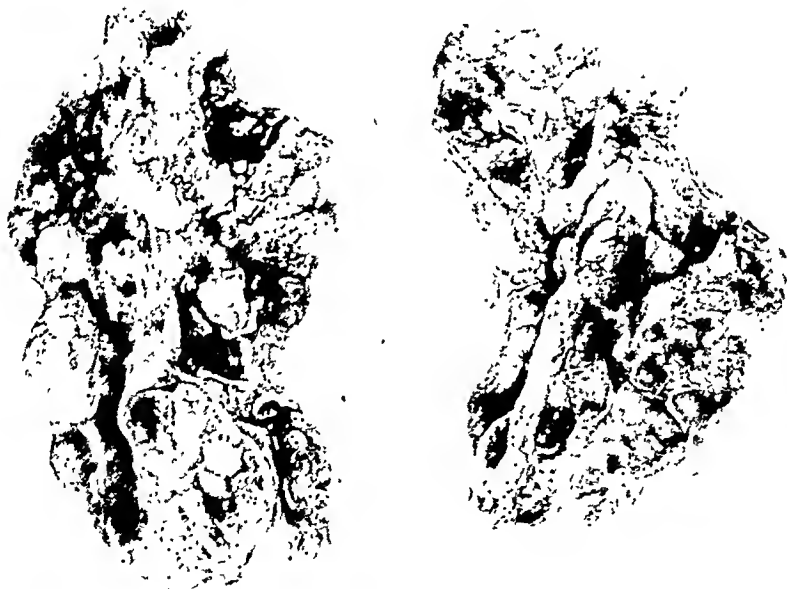


Fig. 5.—Left and right adrenal, respectively. Note the extreme nodularity of the cortex.

The alimentary tract was normal. The liver (weight, 886 grams) was slightly enlarged and fatty. The pancreas (weight, 58 grams) was normal in size. Typical patchy, chalky-white areas of fat necrosis were present both about the periphery and in the substance of the gland. This was most marked in the tail, the left periadrenal fat, and around the upper pole of the left kidney which areas were adjacent to operative site. The spleen was normal. The kidneys were normal except for fat necrosis about the upper pole of left kidney. The uterus and tubes were normal preadolescent. The ovaries were slightly enlarged (length, 3 cm.). Numerous small follicles were visible under the peritoneal surface. Cancellous bone removed from the lumbar vertebra was softer than usual but there was no gross abnormality of the bony trabeculae. The brain was normal. The pituitary (weight, 338 milligrams) appeared normal in size and shape. The left adrenal (weight, 4.7 grams) removed at operation showed the same extraordinary appearance as the right (weight, 5.3 grams). They were both approximately normal



Fig. 6.—Photomicrograph, left adrenal, low power, hematoxylin and eosin stain. A large nodule of hyperplastic tissue has "invaded" the periadrenal fat. Another nodule of hyperplastic cortical tissue is present within the adrenal cortex.

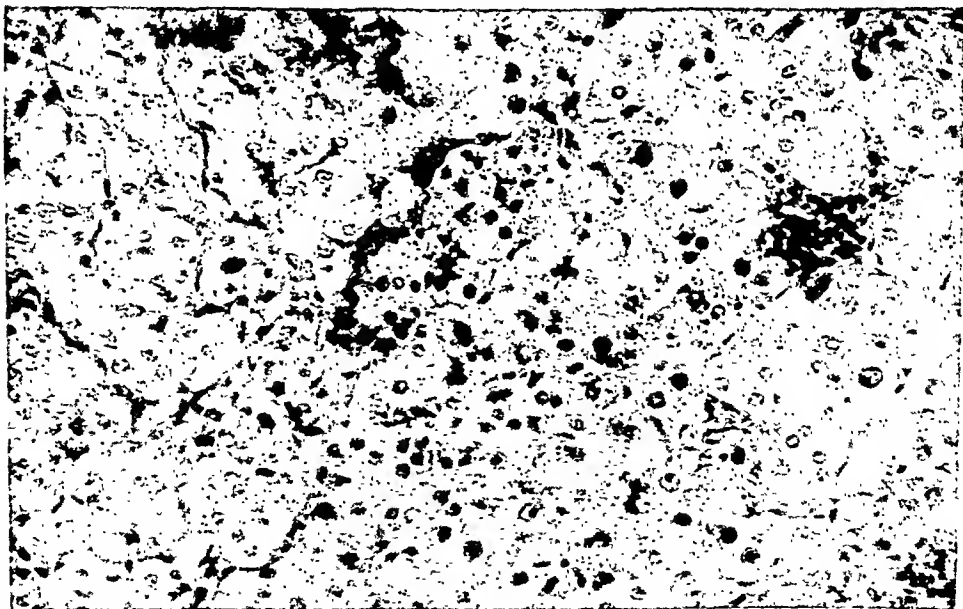


Fig. 7.—Photomicrograph, left adrenal, medium power, hematoxylin and eosin stain. Hyperplastic cortical cells. The cytoplasm of the cells to the left is vacuolated due to lipid content. A focus of lymphocytic infiltration is shown.

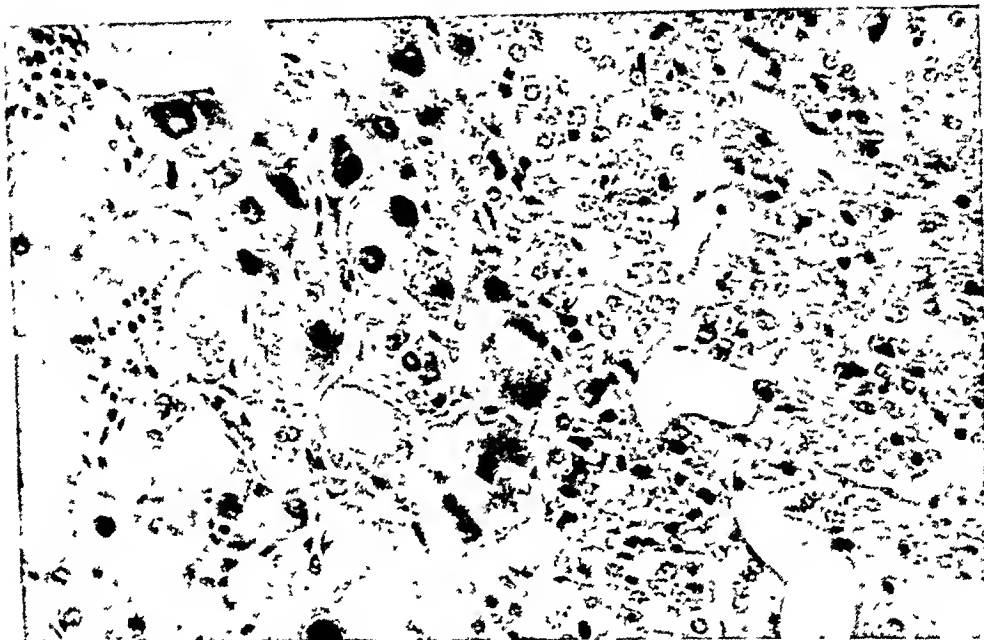


Fig 8—Photomicrograph, right adrenal, medium power, hematoxylin and eosin stain. Note the hyperplastic giant cortical cells. No mitotic figures were seen.

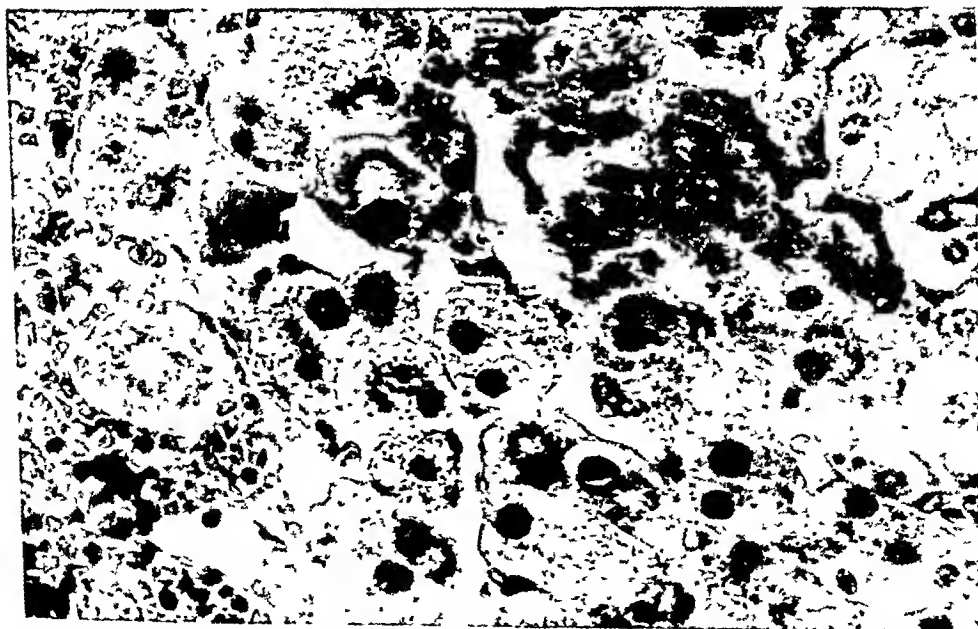


Fig 9—Photomicrograph, right adrenal, medium power, hematoxylin and eosin stain. Giant cortical cells. In some of the cells the lipochrome pigment is present in a curious ring pattern.



in size and shape but the cortical surfaces were studded with numerous smooth, round, globular excrescences varying in size from 1 to 5 mm. (Fig. 5). These nodules shaded in color from dull yellow to dark brown-red, imparting to the glands a peculiar irregular variegated appearance. The cut surface of the adrenals revealed that the nodules were solid and appeared circumscribed. They obviously originated in the cortical tissue and had displaced and replaced the major portion of the normal cortex, the remnants of which could be seen between the nodules. At operation the surgeon removed from the left periadrenal fat numerous (fifteen to twenty) small hemorrhagic nodules 1 to 2 mm. in diameter. Microscopic sections revealed that most of these were small localized areas of hemorrhage but three contained tiny masses of hyperplastic adrenocortical tissue. At the post-mortem examination a careful search was made for more of these nodules in the neighborhood of the operative site and around the right adrenal, but none were found.

*Microscopic Examination.*—

*Adrenals:* In all sections studied there were numerous adenomatous nodules of hyperplastic adrenal cortical tissue, some of which had expanded through the capsule of the gland and had invaded the surrounding fat (Fig. 6). Between the nodules there were areas of normal appearing adrenal cortex which, however, represented only a small proportion of the total cortical tissue. The cortical tissue comprising the hyperplastic adenomata presented a bizarre and variegated picture. The cortical cells varied tremendously in size, shape, and staining qualities and most were larger than the normal. In some, the cytoplasm was abundant and eosinophilic; in others, it was replaced by large amounts of lipid (Fig. 7). Many of these abnormal cortical cells were giant forms with irregular, distorted, dark-staining nuclei (Fig. 8). In many of the giant cells there were cytoplasmic deposits of yellow-brown lipochrome pigment which occasionally was arranged in a peculiar ring pattern (Fig. 9). Mitotic figures were not encountered in spite of the hyperplastic appearance of these cortical adenomata. Scattered throughout the adenomata were focal accumulations of lymphocytes. In spite of the unusual variation in the size, shape, and staining qualities of the hyperplastic adrenal cells, and extension beyond the capsule of the adrenal, they did not appear to have undergone malignant change. The numerous small nodules removed by the surgeon from the left periadrenal fat were for the most part composed of recent hemorrhage. A few contained nodules of the peculiar hyperplastic adrenal cortical tissue identical with that in the adrenals proper. These were considered to be adrenal rests which had undergone the same hyperplastic change as had occurred in both adrenal cortices rather than metastatic deposits as a result of malignant change in the adrenal cortical tissue. Sections of the adrenal were stained by the ponceau-fuchsin method recommended by Broster and associates<sup>24</sup> and none of the fuchsinophilic material was present.

*Pituitary:* The gland was sectioned serially and no adenoma was found. Typical Crooke's changes were present in the majority of the basophiles of the anterior lobe (Fig. 10). The degree of the loss of granularity or hyalinization varied from cell to cell but completely normal appearing basophile cells could be found only in the region adjacent to the pars intermedia. The pars posterior and pars intermedia were normal.

*Brain:* In view of Heinbecker's<sup>25</sup> work, particular attention was paid to the hypothalamic area of the brain. Numerous blocks were taken through this region, including the paraventricular and supraoptic nuclei. No significant lesions were encountered. The pineal gland was normal.

*Pancreas:* Scattered foci of typical fat necrosis were present in the pancreas and peripancreatic fat. Islet tissue was normal in amount. Differential stain showed no abnormal variation in the granulations of either the  $\alpha$  or  $\beta$  cells.

*Liver:* There was excessive accumulation of fat in the liver cells with a predilection for the midzonal area of the liver lobule.

*Kidneys:* No abnormal changes were discernible in spite of the terminal anuria.

*Bone:* Sections of the vertebrae showed the bone trabeculae to be more widely spaced and more delicate than normal but otherwise not unusual. The marrow was normal.

*Breast:* There was proliferation of the ducts but no evidence of acinar proliferation (Fig. 11).

The heart, lungs, spleen, thymus, thyroid, uterus, tubes, and ovaries were within normal limits. Unfortunately, the parathyroids were not obtained.

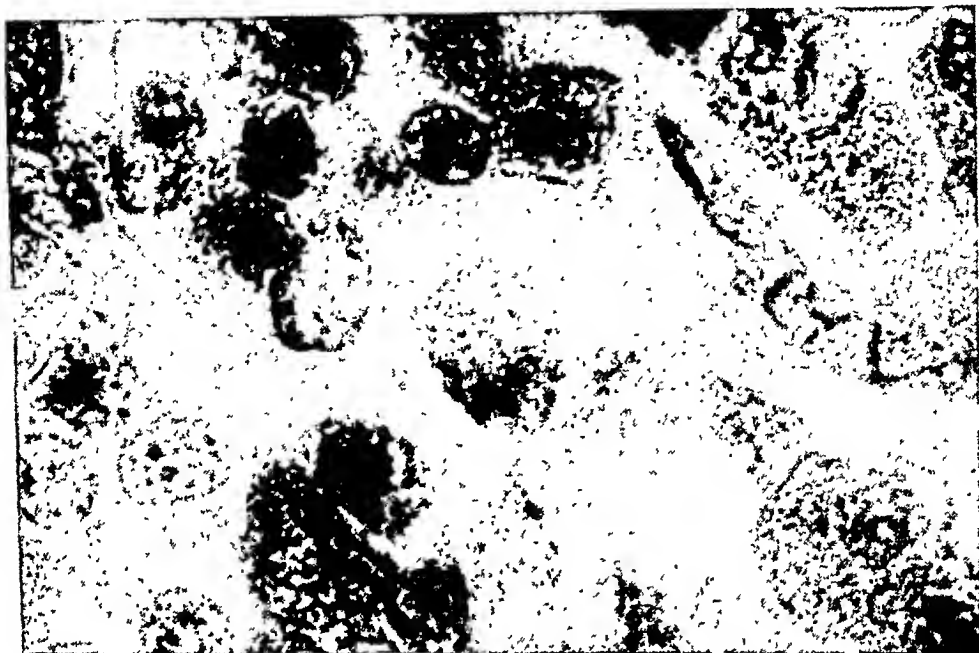


Fig. 10.—Pituitary gland, oil immersion, Mann's stain. In the center is a basophile with typical Crooke's hyaline change. A few basophilic granules are present at one side of the nucleus and a clump at the periphery of the cell.



Fig. 11.—Breast, low power, hematoxylin and eosin stain. There is duct proliferation but no development of acinar tissue.

TABLE I. CLINICAL AND POSTMORTEM FINDINGS

CLINICAL															
NO. AUTHOR OF CASE	YEAR OF PUBLICATION	SEX	DURATION OF SYMPTOMS (YEARS)	AGE AT DEATH (YEARS)	TYPICAL OBESITY	PLETHORA	LINEA ATROPHICA	HIRsutISM	VIRILISM	BLOOD PRESSURE	OSTEOPOROSIS	MUSCULAR WEAKNESS	DECREASED SUGAR TOLERANCE	POLYCYTHEMIA	URINARY EXCRETION OF HORMONES
1. Bauer and Wassings <sup>8</sup>	1913	M	1/2	16	+	+	+	+	-	180	+				Prolan normal  

\*Post-mortem findings not published; pituitary examined by Eisenhardt.<sup>8</sup>†Unable to find published data of complete post-mortem examination.<sup>27</sup> Case cited by Farber et al.<sup>17</sup>

## FIFTEEN CASES OF CUSHING'S SYNDROME IN CHILDREN

POST MORTEM									
ADRENAL CHANGES	PITUITARY TUMOR	CROOK'S CHANGES	HYPOTHALAMUS	INTERNAL GENITALIA	THYROID	PARATHYROID	THYMUS	PANCREAS	KIDNEYS
Enlarged: total wt., 20.6 Gm.	Basophile adenoma			Large testicles	Enlarged	Normal	Atrophy		Nephritis
Normal	None	+		Normal	Large		Carcinoma	Normal	Normal
	Basophile adenoma	+		Normal	Normal				"Scarring"
	None	±							
Normal	Basophile adenoma	+			Normal	Normal		Acute pan'itis	
Hypoplasia	Basophile adenoma	+		Atrophy of gonads	Normal	Fatty atrophy	Large 75 Gm.	Islets increased	Nephritis
Carcinoma left adrenal	None	+							
Hypertrophy: total wt., 15 Gm.	Adenoma, ant. lobe, type?			Infantile	Normal		Atrophy	Fat necrosis	
Well developed	Basophile adenoma			Atrophy of gonads		Atrophy	Atrophy		Nephritis
Carcinoma of cortex, left	None	+							
Carcinoma of cortex, right	Cyst pars intermedia			Infantile			Normal		Normal
Endocrine carcinoma left	None								
Carcinoma of cortex, right	None	+		Interstitial tissue increased	Normal				Nephritis?
Right hypertrophy left atrophy	Basophile adenoma	+	+	Suppressed spermatogenesis		Fat involution	Atrophy	Islets increased	
Tumor left adrenal	None				Advanced for age		Atrophy	Islets increased	Normal
Right carcinoma	None								
Left small									
Left carcinoma	None	+					Atrophy		
Right hypoplasia									
Bilateral hyperplasia	None	+	-	Enlarged ovaries	Normal		Atrophy	Fat necrosis	Normal

## CASE SUMMARY

A typical clinical case of Cushing's syndrome in a girl 8 years of age, who died approximately two days after the removal of one adrenal, is described. In addition to the somatic stigmata of this syndrome the main pathologic changes were: Crooke's changes in the pituitary gland, bilateral nodular hyperplasia of the adrenal cortex, fatty liver, and osteoporosis. An operative complication was pancreatic fat necrosis. The presence of numerous, small, nodular hemorrhages occurring in close proximity but not actually in the operative site was sufficiently unusual that the surgeon removed some of them for section. It is probable that these were an index of the extreme lability of the tissue to injury and hence may account for the development of the pancreatic fat necrosis.

## PATHOLOGY OF CUSHING'S SYNDROME IN CHILDREN

Of the thirty-three cases of Cushing's syndrome or basophilism reported in children, eighteen have come to post-mortem examination. In Table I the significant clinical and pathologic features of the eighteen autopsied cases have been summarized. It is seen that the clinical pattern in children diverges in no fundamental way from that encountered in adults. Likewise, the pathologic changes show the same general trends and variations as found in adults.

In an attempt to assess the pathogenesis of this obviously metabolic disease, aberrations in the physiology of the adrenals and/or the pituitary are usually postulated. From Table I the following facts emerge in respect to the pathologic changes found in basophilism.

1. Crooke's hyaline changes in the basophiles of the pituitary were present in all cases in which the pituitary was examined and these lesions were specifically mentioned. Present in eleven cases, not mentioned in seven.

2. Pituitary adenomata were frequent but not constant: present in a total of seven cases; basophilic in type in six; and in one case not specified.

3. Presumptive histologic evidence of adrenal overactivity was present in thirteen cases of the eighteen. Carcinoma of adrenal cortex in eight, hyperplasia in five. In two the adrenals were stated to be normal and in two the condition of the adrenals was not mentioned.

In addition, the following are frequently associated findings which may or may not be significant:

1. Occasionally there is evidence of stimulation of the gonads but more often the changes are retrogressive.

2. The nerve cell changes present in the hypothalamic region in Heinecker's case were not present in ours. The presence or absence of lesions in this area were not mentioned in any other report.

3. Increase in the number of islets of the pancreas was noted in three cases. Pancreatic fat necrosis was present in three operative cases. Albright<sup>19</sup> has drawn our attention to the prevalence of this complication following operation in cases of basophilism.

4. Nephritis is common. Of the eight cases in which the condition of the kidneys was mentioned, it was present in four.

## DISCUSSION

Cushing was the first to focus attention on the syndrome which now bears his name. He was impressed with the presence of basophile tumors in the pituitary gland of the patients he studied, and thought that they were the cause of the condition. Later work failed to confirm the presence of a pituitary tumor in many undoubted cases of this disease and attention became directed to the adrenal cortex because of the frequency of associated abnormalities of this gland. Crooke's work, in which he demonstrated hyaline changes in the cytoplasm of the basophile cells, again emphasized the importance of the pituitary in any consideration of this syndrome.

In reviewing the changes which are encountered in this condition most of the more important ones seem to be best explained on the basis of adrenal cortical overactivity. The chief exponents of this theory are Albright,<sup>2</sup> Kepler,<sup>6</sup> and Soffer.<sup>29, 30</sup> However, it is possible that the pituitary, by means of the adrenocorticotrophic hormone, initiates the changes, or it may be, as Kepler suggests, that the pituitary changes are secondary to adrenal-cortical overactivity.

Three major effects have been ascribed to the adrenal cortex: (1) regulation of salt metabolism; (2) regulation of carbohydrate metabolism; (3) interaction with the gonads in the sexual development of the individual, which action is probably associated with changes in nitrogen metabolism.

Hyperfunction of the adrenal cortex may be associated with diffuse hyperplasia, benign adenoma, or a neoplasm of the adrenal cortex. Clinically there are two distinct syndromes which may occur as a result of hyperadrenocorticism: (a) the adrenogenital syndrome and (b) Cushing's syndrome.

The adrenogenital syndrome is the result of an overproduction of a masculinizing hormone(s) possibly closely related to the N hormone(s) of Albright. There is apparently little upset in general metabolism with the exception of excessive tissue development (i.e., nitrogen retention). In the male individual this produces premature sexual development and in the female it may produce pseudohermaphroditism if the androgenic principle is overactive during intrauterine life, and pseudoprecocity and masculinization if the stimulation occurs subsequent to birth.

In a pure Cushing's syndrome there is no evidence of true masculinization such as alteration of the voice or enlargement of the clitoris in the female; however, there are many other changes such as obesity, osteoporosis, and disturbed carbohydrate metabolism, which are not encountered in a pure adrenogenital syndrome. It is obvious that in some cases the overactivity of the adrenal cortex is associated with a syndrome which is a mixture of the adrenogenital complex and Cushing's syndrome. Many of the cases collected by Marks, Thomas, and Warkany<sup>7</sup> fall into this group.

In the Cushing's syndrome which especially concerns us here the major findings are related to an abnormal metabolic picture. The most exhaustive attempt to explain the clinical and chemical change encountered in this disease is that of Albright.<sup>2</sup> He has put forth the theory that hyperadrenocorticism with respect to the "S" or sugar hormone is the cause of this disease. He considers

the action of this hormone to be *antianabolic* rather than *catabolic* in nature. Hence the basic condition, he argues, is not an increased destruction of, but rather a failure to produce, tissue. The thin skin, lack of muscle, even the osteoporosis, are thought to be due to a deficient laying down of protein.

The "S" hormone is known to favor the conversion of protein to amino acids. Some of these may become available for conversion to carbohydrate. This, together with the fact that the "S" hormone interferes with the oxidation of carbohydrate, accounts for the low carbohydrate tolerance in these cases.

The hirsutism and moderately elevated 17-ketosteroid excretion in the urine he explains on the basis of a compensatory increase in the "N" (nitrogen) hormone(s) of the adrenal. This hormone(s) causes increased tissue formation and would tend to restore the normal physiologic balance.

The beneficial effects of testosterone in these cases he explains by the fact that it produces the same effects as the "N" hormone in building tissue. Indeed, the two hormones may be closely related chemical compounds.

Albright has postulated hyperadrenocorticism to explain the findings in Cushing's syndrome. He has had to include two hormones producing opposite effects to account for the major findings. Up to the present at least twenty-five active principles have been isolated from the adrenal cortex.<sup>20</sup> Undoubtedly many more will be discovered. It seems likely to the authors that while Albright's statement of the case gives the broad outline of the picture, the detailed interpretation will depend on the correlation of the activity of all these various substances. An illustration of this is provided by the different effects produced by whole adrenal cortical extract and desoxy corticosterone. Hypertension and increased salt retention can be brought about by excessive administration of desoxy corticosterone but not by administration of the whole extract.

It was seen, therefore, that in whole adrenal cortical extract there is a balancing effect between the various substances, one upon the other, while in Cushing's syndrome there is some alteration in the proportion of these components. The extent of these alterations may vary from one patient to another. Thus, in the cases which have been reviewed there was considerable variation in the extent of clinical findings. For example, in some patients, virilism, as indicated by hirsutism and enlarged genitalia, was marked, though in the majority hirsutism without genital enlargement was the rule. In some, osteoporosis was marked; in others, it was less prominent. Some had a definite diabetes; others had only mild signs of carbohydrate intolerance. The same may be said for any of the other features of the disease. These variations tend to support the theory that there are a number of substances that may be abnormally active.

On the other hand, the fact that such a uniform clinical picture is presented in this disease, argues for some fundamentally similar change in all cases. The possibility arises that this fundamental change may be due to some abnormal substance elaborated by the adrenal, but so far there is no proof for this hypothesis. Since many of the findings can be explained by known effects of adrenal extracts, it seems more likely that some derangement of the normal mechanism is at fault. At present we have insufficient knowledge to draw a complete picture of what these changes are.

While the preceding discussion has assumed that the adrenal is the seat of the disorder, a view which is ably defended by Kepler,<sup>6</sup> there is still the possibility that the pituitary is the initiating factor. Kepler argues that the almost universal finding of Crooke's changes in the basophile cells of the pituitary is a secondary, rather than a primary effect. In support of this he points out that removal of an adrenal tumor such as a carcinoma has caused a remission in the symptoms of the disease. On the other hand the absence of demonstrable changes in the adrenal in some cases has made it difficult to incriminate this organ as the cause of the disease in every case.

A recent article by Conn, Louis, and Wheeler<sup>31</sup> throws some additional light on the interrelationships between the pituitary, adrenal cortex, and the metabolism of carbohydrates and protein. These authors produced a diabetic state in all of three normal subjects by daily intramuscular injections of purified pituitary adrenocorticotrophic hormone. In addition, two of the subjects developed a negative nitrogen balance during the period of hormone administration, despite an adequate protein intake. These findings would appear to favor Albright's contention that the metabolic disturbances of Cushing's syndrome are mediated through the adrenal cortex. However, it cannot be gainsaid that in some cases, particularly when there is bilateral hyperplasia of the adrenal cortices, the initiating stimulus may arise in the pituitary.

That there is a marked interdependence of the adrenal and pituitary glands upon each other is well known, and the apparent beneficial effect of irradiating the pituitary in Jamin's<sup>26</sup> case may be explained on this basis.

Heinbecker<sup>13</sup> has described changes in the hypothalamic nuclei and thinks there may be a relationship between these findings and the basophile hyaline changes. He suggests that these hypothalamic changes may bear a causal relationship to the disease. No other authors have described these changes and none was found in our case.

The treatment of these cases presents many problems. Since reports of cures following removal of an adrenal tumor have been published, it was decided to explore our patient with the hope of removing an adrenal tumor if one were present. At operation an obviously abnormal adrenal was found on the left side. Palpation of the right adrenal at this time indicated to the surgeon a gland of apparently normal size. Consequently, the abnormal left gland was removed. It was felt that a similar condition might be present on the right but by the removal of one abnormal adrenal it was hoped that some measure of improvement might be gained. Had the patient survived, testosterone therapy as suggested by Albright was contemplated. The reason for this patient's death is not clear, since her sudden fall in blood pressure did not occur until twenty-four hours after her operation. Whether the acute pancreatic necrosis was the cause of the acute circulatory collapse is a matter of conjecture. It is generally known that these patients are a poor operative risk and that death often occurs for no apparent reason.

As the life expectancy of untreated patients is not great, and because of their increasing physical deformity, radical measures of treatment may be justified. However, the treatment of these patients should be undertaken accord-



ing to a set programme. The reader is referred to Soffer's article<sup>30</sup> for details of this procedure.

#### SUMMARY

The literature of Cushing's syndrome or basophilism in children has been reviewed with particular reference to the seventeen cases which have come to post-mortem examination.

An additional case in an 8-year-old white girl is reported, together with the clinical and post-mortem findings.

The majority of the clinical and experimental evidence at present available suggests that the physiologic and pathologic changes in this syndrome are due to an imbalance of the hormones of the adrenal cortex. However, the role of the pituitary as a causative or initiating factor cannot be entirely discounted, in view of the fact that the hyaline change in the basophiles of this gland is the most constant pathologic change in this disease.

Further knowledge must be gained before this condition is thoroughly understood and before adequate treatment can be given.

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## OBSERVATIONS ON THE USE OF PROCAINE-PENICILLIN

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**I**N ORDER to obtain prolonged high serum penicillin titers following a single injection, a number of different penicillin preparations have been developed. All such preparations must be shown to be nontoxic and must be capable of maintaining therapeutic serum penicillin titers for a prolonged period following a single injection. Procaine-penicillin is one of the newer preparations, and the purpose of this report is to record our findings in its clinical use.

### METHOD OF STUDY

The procaine-penicillin used is marketed as Duracillin and was kindly furnished by Eli Lilly and Company.\* It is a crystalline salt of procaine penicillin-G, suspended in sesame oil.<sup>1</sup> It remains in a fluid state at room temperature and is quite stable. Each cubic centimeter contains 300,000 units of penicillin and 124.5 mg. of procaine base. A dry syringe and a 20-gauge needle are used for intramuscular injection.

Serial serum penicillin titers following a single injection of Duracillin were determined in a group of thirteen well children. The subjects were of varying weights and ages. No attempt was made to calculate the penicillin dosage by an exact number of units per unit of body weight. Instead, an arbitrary amount of 150,000 units was given to infants under 11 kg. body weight, and 300,000 units were given to children over this weight. Blood was drawn at varying intervals following a single injection of Duracillin and serum penicillin titers were determined by a tube dilution method using FDA *Staphylococcus aureus* 209P as the test organism. In most instances penicillin titers were not carried above 1.0 or 2.0 units per c.c., as this was not felt necessary for the purposes of this study.

### RESULTS

Penicillin titers obtained in ten normal children following one injection of Duracillin are outlined in Table I. Twelve hours after injection, the penicillin titers were greater than 1.0 unit per cubic centimeter in seven cases. In two instances the titer was 0.2 unit per cubic centimeter, and in only one was the titer 0.1 unit per cubic centimeter. In no case was a level of less than 0.1 unit per cubic centimeter found twelve hours after injection. Twenty-four hours after injection titers were determined in eight of these patients and in seven instances varied from 0.1 to 1.0 unit per cubic centimeter. In only one patient was a titer of less than 0.1 unit per cubic centimeter found. A few variations are seen in titers of Patients 4, 8, and 9, where a low titer is followed by a higher

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one. These could be due to mechanical factors influencing absorption. In two of the three instances, a borderline reading in the next lower tube produced this apparent variation.

TABLE I. SERUM PENICILLIN TITER IN UNITS PER CUBIC CENTIMETER AFTER ONE DURACILLIN INJECTION IN NORMAL CHILDREN

PA- TIENT	WEIGHT (KG.)	PENI- CILLIN (UNITS)	HOURS AFTER INJECTION									
			1	2	4	8	12	16	18	20	24	
1	4.7	150,000	—	—	>2.0	—	>2.0	—	—	1.0	1.0	
2	5.5	150,000	—	>1.0	—	—	>1.0	0.5	—	0.2	0.1	
3	5.9	150,000	—	>1.0	>1.0	>1.0	>1.0	—	1.0	—	—	
4	8.0	150,000	—	—	>1.0	—	>1.0	0.5	—	1.0	0.2	
5	23.0	300,000	—	>1.0	>1.0	>1.0	>1.0	—	0.5	—	—	
6	26.0	300,000	—	—	>1.0	—	>1.0	>1.0	—	0.5	0.2	
7	34.5	300,000	—	—	0.5	—	0.2	0.2	—	0.1	0.1	
8	35.0	300,000	—	—	0.5	—	0.2	0.5	—	0.5	0.2	
9	38.0	300,000	—	—	>1.0	—	>1.0	>1.0	—	0.2	1.0	
10	42.0	300,000	—	—	0.5	—	0.1	0.1	—	<0.1	<0.1	

Table II records serum penicillin titers in three patients at more frequent intervals following one injection of Duracillin. Very rapid penicillin absorption is manifest with titers of 1.0, 2.0, and 6.5 units per cubic centimeter being found one-half hour after injection. The peak level was found one hour after injection in two patients and one-half hour after injection in the third. Eight hours after injection the titers ranged from 0.5 to 1.0 unit per cubic centimeter. After twenty-four hours two patients had less than 0.1 unit per cubic centimeter, although one had 1.0 unit per cubic centimeter.

TABLE II. SERUM PENICILLIN TITERS AT INTERVALS AFTER INJECTION OF DURACILLIN IN THREE CHILDREN

PATIENT	WEIGHT (KG.)	PENICILLIN (UNITS)	HOURS AFTER INJECTION						
			$\frac{1}{2}$	1	2	4	8	12	24
1	6.6	150,000	2.0	4.0	2.0	1.0	0.5		0.1
2	13.5	150,000	1.0	>1.0	1.0	0.5	0.5	0.5	0.1
3	13.5	300,000	6.5	5.0	4.0		1.0		1.0

In both Tables I and II there is no exact correlation between serum penicillin titers and the amount of penicillin administered. In general, however, higher titers were found in patients who received relatively larger amounts in proportion to body weight.

#### THERAPEUTIC RESULTS

Forty-one sick children were treated exclusively with Duracillin. They are classified as follows: those with otitis media and nasopharyngitis, 6; bronchiolitis, 5; bronchopneumonia, 5; laryngotracheobronchitis, 6; cellulitis and adenitis, 2; acute tonsillitis, 4; conjunctivitis, 1; lobar pneumonia, 5; osteochondritis, 1; congenital syphilis, 1; subacute bacterial endocarditis, 1; upper respiratory infection, 4. Children who were moderately or severely ill were given penicillin in the above outlined amounts every twelve hours until clinical improvement was noted, after which the injections were given at twenty-four hour intervals.

In Table III are summarized penicillin titers found in this group of sick children treated with Duracillin. These titers varied from 0.2 to 4.0 units per cubic centimeter twelve hours after injection. Twenty-four hours after injection the levels varied from less than 0.1 to 1.0 per cubic centimeter. Most of the twenty-four-hour levels ranged from 0.1 to 0.2 unit per cubic centimeter with only one instance in which a level of less than 0.1 unit per cubic centimeter was found. The highest levels were found in the three-week to nine-month and in the thirteen-month to five-year age groups. These two groups received the largest amount of penicillin relative to body weight. Clinical therapeutic results were in no manner different from those obtained in similar groups of patients treated in the usual manner with regular crystalline penicillin.

TABLE III. SUMMARY OF PENICILLIN TITERS IN FORTY-ONE PATIENTS TREATED WITH DURACILLIN

NO.	WEIGHT (KG.)	AGE	PENICILLIN (UNITS)	SERUM TITERS UNITS/C.C.	
				12 HOURS	24 HOURS
12	3.1 to 8.0	3 weeks to 6 months	150,000	1.0 to 4.0	0.2 to 1.0
7	6.9 to 10.8	7 months to 12 months	150,000	0.2 to 2.0	0.1 to 0.2
14	10.1 to 18.8	13 months to 5 years	300,000	1.0 to 2.0	0.1 to 1.0
8	18.8 to 31.5	5½ years to 9 years	300,000	0.2 to 0.5	<0.1 to 0.5

A total number of injections in this series was 320. In addition, approximately 1,000 injections have been given to other children in the St. Louis Children's Hospital, the St. Louis City Hospital, and in the outpatient clinics. There has been one case in which a sterile abscess developed. This resolved spontaneously without open drainage. Dr. Virgil Scott<sup>2</sup> has used this material in outpatient treatment of 102 adults with active or latent syphilis. Five of these patients showed definite toxic manifestations. Four had an urticarial or papular skin eruption which was promptly relieved by the administration of Pyribenzamine. The fifth patient had a more severe reaction with nervousness, apprehension, a feeling of tightness in the chest, numbness in the extremities, and headache.

It has been shown by Lief and co-workers<sup>3</sup> that procaine is hydrolyzed both in vitro and in vivo to p-aminobenzoic acid and diethylaminoethanol. As very small amounts of p-aminobenzoic acid are capable of inhibiting the action of a much larger amount of sulfonamide drugs, the question naturally arises as to whether simultaneous administration of procaine-penicillin with sulfonamides might not result in a diminution or total absence of sulfonamide effect. Until this is shown not to be the case, it would seem unwise to give the two drugs simultaneously in the treatment of infections.

In an attempt to settle this point, a group of children were given Sulfamerazine for three days. On the first and third days Sulfamerazine alone was administered but on the second day two injections of procaine-penicillin were given, twelve hours apart. Two blood specimens were obtained each day and tested against a sulfonamide-sensitive test organism. We have been able to show an inhibitory effect on the test organism of sera containing Sulfamerazine. This inhibition in some cases diminished or was lost following the injection of procaine-penicillin even though the colorimetrically determined serum sulfon-

amide levels were unchanged. However, in fifty tests performed on more than thirty sera, results were not consistent, so that other techniques will need to be devised before this phenomenon can be accurately evaluated.

### CONCLUSIONS

Procaine-penicillin in the form of Duracillin has been used in both well and sick children. A standard dosage of 150,000 units was given to children under 11 kg. body weight, and 300,000 units were given to children over this weight. Adequate therapeutic serum penicillin titers of 0.1 unit per cubic centimeter or more were obtained in all patients studied twelve hours after injection. In the great majority of patients titers of 0.1 unit per cubic centimeter or more were found twenty-four hours after a single injection.

Injection every twelve hours should be used when high serum titers are desired and every twenty-four hours where a level of approximately 0.1 to 0.2 unit per cubic centimeter is sufficient.

Because of very rapid absorption with peak serum titers one-half to one hour after injection, it is not necessary to give an initial dose of plain crystalline penicillin.

As long as there is a possibility of inhibition of sulfonamides by p-aminobenzoic acid derived from the procaine, it is felt that plain crystalline penicillin should be used in the more severe infections where the sulfonamide drugs must be concomitantly employed.

Undesirable toxic reactions in children are very infrequent. No evidence of sensitization to either penicillin, sesame oil, or procaine was seen. One instance of sterile abscess formation was encountered. This lack of generalized toxic reactions in children is sharply contrasted to the reactions seen in a group of adults similarly treated, where five out of 102 patients showed evidence of sensitization. In these patients, Pyribenzamine successfully relieved the allergic manifestations, and at a later date when given prophylactically prior to subsequent injections of procaine-penicillin, no allergic reactions were observed.

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# PATHOLOGIC FINDINGS IN THE NEONATAL PERIOD

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ALTHOUGH approximately 5 per cent of all deaths occur during the neonatal period,<sup>1</sup> i.e., the first month of extrauterine life, many pathologists and clinicians have little interest in investigating these deaths. All too often the deaths are attributed solely to prematurity or atelectasis, neither of which is an adequate primary cause of death.<sup>2, 3</sup> This paper is presented in order to emphasize the fact that an adequate cause of death can be demonstrated in the majority of infants dying within the first month of life. This has been repeatedly demonstrated<sup>4-6</sup> but is still not generally appreciated.

The material for the present paper consists of the consecutive autopsy records of 50 live-born infants dying on the Tulane Service of the Charity Hospital of Louisiana at New Orleans. Infants weighing less than 500 Gm. at the time of delivery were excluded. Fourteen infants were previsible premature infants (weight, 500 to 999 Gm.), 23 were viable premature\*infants (weight, 1,000 to 2,499 Gm.) and 8 were full-term infants (weight 2,500 grams or more). Their ages varied from 5 minutes to 25 days; 33 died within 24 hours of delivery; only 9 lived 7 days or more. Forty infants were Negro and ten were white. An adequate cause of death was demonstrated in 43. Asphyxia was responsible for ten deaths, intraventricular hemorrhage for 10, bronchopneumonia for 7, congenital syphilis for 5, congenital anomalies for 4, and miscellaneous lesions were held accountable for the death of 7 infants (Table I).

TABLE I

CAUSE OF DEATH	CASES
Asphyxia	10
Intraventricular hemorrhage	10
Bronchopneumonia	7
Miscellaneous	7
Undetermined	7
Congenital syphilis	5
Congenital anomalies	4
Total	50

Eight of the ten infants who died as a result of asphyxia were premature. One infant lived for twenty-seven hours, all of the others died in less than one day. The gross findings at autopsy in an infant dying of asphyxia consist of multiple petechiae and marked venous congestion.<sup>6</sup> In the present series the diagnoses have all been confirmed by microscopic examination. The histologic diagnosis of asphyxia is based on the presence of large amounts of amniotic sac contents in the pulmonary alveoli. These appear free in the alveoli as blue or, less often as pink, elongated, fusiform and twisted cornified epithelial cells, usually non-nucleated, derived from the skin of the fetus (Fig. 1). At

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other times, and especially in premature infants, a pink hyaline material may be present as a distinct membrane applied to the alveolar surfaces (Fig. 2); this material is thought by some to be vernix caseosa.<sup>6, 7</sup> Occasionally lanugo hairs or meconium may be present within the pulmonary alveoli.

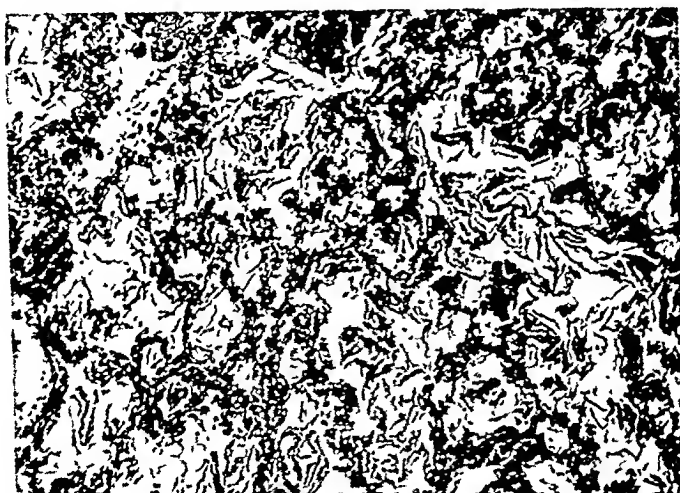


Fig 1—Lung showing large numbers of cornified epithelial cells in the alveolar spaces ( $\times 175$ ).

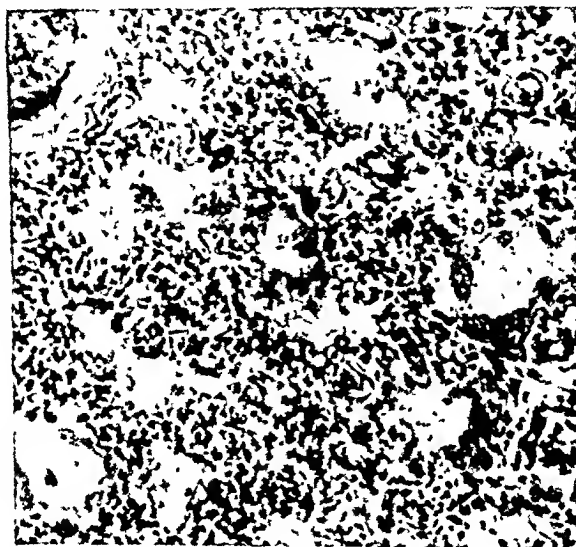


Fig 2—Lung showing asphyxial membrane ( $\times 175$ )

The presence of amniotic sac contents within the alveoli of the lungs is a result of intrauterine respiration. Whether such respiration occurs under normal circumstances or whether it is dependent upon intrauterine asphyxia is a moot question.<sup>8-11</sup> However, regardless of the presence or absence of normal intrauterine respiratory movements, most authors agree that the presence of large amounts of amniotic debris within the lungs is indicative of fetal asphyxia.<sup>6, 12</sup>



Intraventricular hemorrhage was responsible for ten deaths. All but one infant in this group were premature, seven of these infants weighed less than 1,300 grams. Maegregor<sup>6</sup> believes that intraventricular hemorrhage in the neonatal period occurs almost exclusively in premature infants. The duration of life in these ten infants varied from 5 minutes to 31 hours; only three lived over 17 hours. In one infant the amount of intraventricular hemorrhage was slight but there was a massive subarachnoid hemorrhage.

The mechanism of production of these hemorrhages is not clear, and Holland<sup>13</sup> has commented on the difficulty of differentiating those caused by asphyxia from those of traumatic origin. The hemorrhage within the ventricles may arise from engorged choroid plexuses or it may follow rupture of a subependymal hemorrhage into the lateral ventricle. These subependymal hemorrhages may attain considerable size, and are usually located about the terminal vein between the caudate nucleus and the thalamus (Fig. 3). Knowledge of these subependymal hemorrhages is important to the clinician handling newborn infants, as improper care may possibly convert a relatively innocuous subependymal hemorrhage into a fatal intraventricular hemorrhage.



Fig. 3.—Coronal section through cerebral hemispheres showing bilateral subependymal hemorrhages

Bronchopneumonia was held responsible for seven deaths in the present series. All of these infants were premature, their weights ranging from 885 to 2,470 grams. Their ages varied from 17 minutes to 24 days, and four of them lived less than 24 hours. Fourteen other infants had varying degrees of bronchopneumonia, but in these it was not thought to be the principal cause of death. Bacteriologic studies were not carried out as most of the infants had died at least forty-eight hours before the autopsy was performed. The infants dying of bronchopneumonia within the first twenty-four hours after birth probably represent examples of antenatal infections.<sup>14, 15</sup> It has already been pointed out that intrauterine respirations may occur, particularly in asphyxi-

ated fetuses, and that these may lead to the aspiration of amniotic sac contents. If the contents of the amniotic sac are infected, as they may be after premature rupture of the membranes, an intrauterine pneumonia may occur. The importance of pneumonia as a cause of death in the neonatal period has been pointed out by others. Macgregor<sup>16</sup> found inflammatory changes in the lungs of 37 per cent of live-born infants surviving up to 28 days and Benner<sup>15</sup> noted inflammatory reactions in the middle ears, sinuses or lungs of 46 per cent of live-born infants dying under the age of 2 days.

Congenital syphilis was responsible for five deaths in the present series. All were premature Negro infants; one lived for 34 hours, and the others died in less than one day. They showed the usual lesions of congenital syphilis, including hepatomegaly, splenomegaly, syphilitic osteochondritis, and syphilitic pancreatitis. One infant presented the clinical picture of hemorrhagic disease of the newborn and one showed syphilitic involvement of the hypophysis.<sup>17</sup> Four of the five infants showed what appeared to be a nonspecific bronchopneumonia. Chase<sup>18</sup> believes that aspiration pneumonia following intrauterine asphyxia is the immediate cause of death in the majority of syphilitic infants who die before the age of one month.

Congenital anomalies were held responsible for the death of four infants. The anomalies were atresia of the bowel, meningomyelocele with associated meningitis, anencephaly, and external hydrocephalus. The latter was associated with congenital absence of the tectum of the midbrain. Fraser and Dott<sup>19</sup> have described two cases of external hydrocephalus associated with congenital absence of the quadrigeminal plate, the superior cerebellar peduncles, and the posterior wall of the aqueduct of Sylvius, with resultant discharge of cerebrospinal fluid directly from the ventricles into the "submeningeal space." The anencephalic infant lived for two days and showed hypoplasia of the adrenals and aplasia of the pars nervosa of the hypophysis, as described by Angevine.<sup>20</sup>

The miscellaneous lesions responsible for death included thromboses of the venous sinuses of the dura mater (three cases), dural tears (two cases) and meningitis (two cases). These infants lived from 2 hours and 11 minutes to 18 days; five of them lived 7 days or more.

#### DISCUSSION

Both clinicians and pathologists should recognize the fact that an adequate cause of death can be demonstrated at autopsy in the majority of infants dying during the neonatal period. Careful postmortem examinations are especially important during this period, when clinical diagnoses are so unreliable.

The high incidence of infection in the present series is noteworthy. Of the fifty infants, some form of infection (bronchopneumonia, congenital syphilis, meningitis, or omphalitis) was present in twenty-five infants, and in fourteen infection (bronchopneumonia, congenital syphilis, or meningitis) was thought to be the primary cause of death. The importance of infections as a cause of neonatal deaths has been emphasized by others but is still not generally appreciated. A clinical diagnosis of many of these infections would be impossible,

but recognition of the fact that infections are common in the neonatal period, occurring even in infants shortly after birth, should aid in lowering neonatal mortality rates.

### SUMMARY

An adequate cause of death was demonstrated at autopsy in forty-three of fifty infants dying during the neonatal period. Asphyxia, intraventricular hemorrhage, and bronchopneumonia were the leading causes of death. Twenty-five of the fifty infants showed inflammatory lesions which, in most instances, were attributable to infection, but in only fourteen of these was infection believed to be the principal cause of death.

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# THE TREATMENT OF AMMONIA DERMATITIS WITH DIAPARENE

## REPORT ON 500 CASES

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IN A preliminary report<sup>1</sup> we suggested the use of a quarternary ammonium compound, para di-isobutyl-eresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate\* for ammonia dermatitis. This method of treatment was based on Cooke's<sup>2</sup> pioneer work, which demonstrated that the ordinary diaper rash is usually an ammonia dermatitis and that "the cause of the ammonia production is directly due to bacterial decomposition of urinary urea into free ammonia, and the principal organism concerned is *B. ammoniagenes*, a saprophytic, gram-positive bacillus which originates in the feces and infests the skin of the diaper region." Cooke further pointed out that "the prevention and treatment of ammonia dermatitis is dependent on preventing bacterial growth, and this is readily accomplished by the use of a nonvolatile antiseptic in the diaper itself."

We reported that para di-isobutyl-eresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate has a marked bactericidal action on *B. ammoniagenes*. Forty-nine out of fifty infants with ammonia dermatitis were cleared within one week by impregnating their diapers with this drug. In a series of tests we were unable to produce any toxic or allergic effects on the skin with solutions of this drug.

We have now reviewed the first 500 cases which were diagnosed as ammonia dermatitis and then treated with Diaparene-impregnated diapers. One tablet to two quarts of water provided an approximately 1:25,000 solution. Up to six diapers were placed in a basin and the solution poured over them. This procedure, if carefully followed, insures approximately equal concentration in each diaper. The drug is absorbed from the solution by the diapers almost quantitatively, irrespective of the concentration of the solution. If the diapers were introduced one at a time, the drug might be absorbed on the first diaper placed in the solution.

Tables I and II give evidence that diapers treated in this fashion are bacteriostatic against *B. ammoniagenes* and *Staphylococcus aureus*. All treated diapers, even after ironing and storage, inhibited the growth of these organisms. Furthermore, samples of all these treated diapers, when incubated in glucose broth for twenty-four hours, showed no growth.

<sup>1</sup>From the Departments of Pediatrics and Bacteriology, New York Medical College, Flower and Fifth Avenue Hospitals.

\*This drug was supplied to us as Diaparene tablets by Homemakers Products Corp., New York, N. Y.

TABLE I. EXTRACT AGAR DEEP INOCULATED WITH TWENTY-FOUR-HOUR BROTH CULTURE STAPH. AUREUS (44) 0.1 C.C. PIECE OF TREATED DIAPER, 1 CM. SQUARE, PLACED ON SURFACE

DIAPERS	ZONE OF INHIBITION		
	A	B	C
3 treated diapers (A, B, C)	+	+	+
3 treated diapers (A, B, C) ironed	+	+	+
3 treated diapers (A, B, C) after storage for two weeks	+	+	+
3 untreated diapers (controls)	0	0	0

TABLE II. EXTRACT AGAR INOCULATED WITH A CULTURE OF B. AMMONIAGENES (ALKALIGENES AMMONIAGENES) 0.1 C.C. PIECE OF TREATED DIAPER, 1 CM. SQUARE, PLACED ON SURFACE

DIAPERS	ZONE OF INHIBITION		
	A	B	C
3 treated diapers (A, B, C)	+	+	+
3 treated diapers (A, B, C) ironed	+	+	+
3 treated diapers (A, B, C) after storage for two weeks	+	+	+
3 untreated diapers (controls)	0	0	0

### RESULTS

We have analyzed the results in 500 cases of diagnosed ammonia dermatitis treated with Diaparene. These cases include hospitalized, clinic, and private patients. All rashes were in the diaper region and there was an associated ammonia odor reported in the diapers. They were divided into mild, moderate, and severe rashes. Erythema was called mild, papulovesicular and pustular lesions were called moderate, and ulcerations were denoted as severe. Of the rashes, 172 were called mild; 204 were called moderate; and 124, severe. Of these infants, 87 also had ulcerations of the external urethral meatus.

Of the cases, 436 which were diagnosed as ammonia dermatitis and treated with Diaparene, cleared promptly within one week. Of the sixty-four which did not clear, forty-three were mild, sixteen were moderate, and three were severe rashes. All but three of the infants with ulcerations of the external urethral meatus were cleared.

Nine of the sixty-four did not return or refused further treatment. The remaining fifty-five failures were reviewed. Twenty-three of these were thought not to have been ammonia dermatitis, but due to irritative or allergic factors. In eleven of these the mother had not prepared the diapers according to instructions. In the other twenty-one cases, we could find no reason for the failure.

### COMMENT

Ammonia dermatitis is the most common rash in the diaper region but there are other possible rashes which may occur in that area. Some of these which confused us were contact dermatitis, atopic dermatitis, acid fecal irritation, and intertrigo. Contact dermatitis was often due to soap, baby oil, and bleach in the diaper. Atopic dermatitis was blamed on the usual milk, wheat, egg, and orange juice. Acid fecal irritation was associated with loose stools and was most marked about the anus. Intertrigo was found in fat babies and was most marked in the folds of the skin. Occasionally it is difficult to differentiate between these and ammonia dermatitis. We have found it practical,

when in doubt, to give a therapeutic trial with Diaparene, since ammonia dermatitis is the most frequent offender. If this fails, we then go into the laborious investigation of the various kinds of contact and atopic dermatitis.

The severe cases of ammonia dermatitis have been secondarily infected with *Staph. aureus* and various streptococci. In these cases best results are obtained by using triple strength Diaparene (three tablets to two quarts of water). In vitro, this stronger concentration has a marked bactericidal action on these organisms.

We have received communications from a few pediatricians who feel that boric acid is still the treatment of choice for ammonia dermatitis. Boric acid is a very weak bactericide and there are many reports<sup>3</sup> of poisoning when applied to the broken or burned skin. We feel that it has outlived its usefulness and should be discarded.

In the past we have followed Cooke<sup>2</sup> in using a 1:4,000 solution of mercuric chloride to impregnate the diapers in ammonia dermatitis. It is an efficient bactericide against *B. ammoniagenes* but has well-known poisonous properties. Our results with Diaparene reveal an even greater efficiency, and, thus far, with no irritant or allergic effects on the skin.

It is of great importance, in using this preparation, to instruct mothers to follow directions carefully. In one case reported to us, the mother by mistake gave her infant orally one tablespoonful of the solution three times daily for one month. Although there were no apparent harmful effects, such accidents emphasize the importance of careful directions on the part of the physician.

#### SUMMARY

1. A review has been made of 500 cases of diagnosed ammonia dermatitis treated with Diaparene-impregnated diapers.
2. This has proved a safe and efficient treatment for ammonia dermatitis.
3. Other rashes occur in the diaper region which may be confused with ammonia dermatitis. Some of these are due to contact dermatitis, atopic dermatitis, acid fecal irritation, and intertrigo.

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# THE PREVALENCE OF COLDS IN NURSERY SCHOOL CHILDREN AND NON-NURSERY SCHOOL CHILDREN

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WHETHER or not there is an actual health risk in the daily exposure of the pre-school child to groups of people, adults or his peers, is frequently a question of debate. This study represents an attempt to evaluate certain effects of group exposure in a nursery school situation. In selecting a certain aspect of health for study, it was decided to measure the prevalence of colds in nursery school and non-nursery school children, because colds represent the largest single cause of school absenteeism at various age levels. Another reason for measuring colds is that they are transmitted by the discharges of the respiratory tract, as are the other common communicable diseases. The control of the common cold is fundamental in any program of disease control in the schools.

In selecting a definition of a cold to be used in this study, various possibilities were considered. Hilding<sup>6</sup> defined the cold as a "widespread, mild, afebrile rhinitis characterized by a copious, thick, mucinous, nasal discharge, and a self-limited course of two to three days." McGee, Andes, Plume, and Hinton<sup>8</sup> regard the cold as a "symptom complex" which may follow irritation of the nose and throat by chemical agents, physical agents, or by infection. In this study the definition given by McGee, Andes, and associates was followed, since no method was available to differentiate factors causing upper respiratory inflammations.

## PROCEDURE

*Subjects.*—The subjects of this study were twenty-five children attending the Purdue University Nursery School and twenty-six children not attending the nursery school whose names had been placed by their parents on its waiting list. All children enrolled from Jan. 15 through April 8, 1946, were to be included. However, due to moves to other cities, frequent or long absences as a precautionary measure, inadequate records, and extended vacations in a different climate, seven of the total enrollment in the nursery school and six of the original thirty-two in the non-nursery school group were omitted from the final study.

The nursery school children were in attendance from 9:00 A.M. to 12:45 P.M. for five days a week. Upon arrival at school each child was checked for any signs of illness by a registered nurse. It was the policy of the school to exclude all children with symptoms such as red, watery eyes, nasal discharge, overfatigue, and/or unusual irritability. If such signs of illness developed during school, the child was isolated or was sent home.

The nursery school children who served as subjects in this study ranged from 29 to 56 months of age. The group consisted of thirteen girls and twelve

boys. As is usual in this type of nursery school, the subjects tended to be above average in intelligence and to come from homes of a relatively high socio-economic level. Twenty had fathers who were in professions and five had fathers who were in business. All but three of this group of children were taking vitamin compounds in some form in addition to their regular diet. Six children were known to have definite allergies and five others had shown allergic manifestations of some type and in various degrees. All of the nursery school children had had a physical examination by the family physician within the eighteen months preceding the study. The health status of twenty-three was rated as "superior" and of two as "average" by the physician. Fourteen children of this group had been to the dentist at least once for filling of cavities, teeth cleaning, or dental checkup.

The non-nursery school children who served as subjects in this study ranged in age from 23 to 52 months. The group consisted of ten girls and sixteen boys. The subjects came from homes of relatively high socio-economic level. Of this group, twenty had fathers who were professional men and six had fathers who were businessmen. All but two of this group were taking vitamin compounds in addition to their regular diet. Three of these children were known to have definite allergies and seven had shown allergic manifestations of some type and in various degrees. All but three had had a physical examination by the family physician within the eighteen months preceding the study. The health status of twenty-three was rated as "superior" by the family physician. Five children of this group had been to the dentist at least once for teeth cleaning, filling of cavities, and dental checkup. The non-nursery school group was selected from the nursery school waiting list on the basis of age. It was possible to pair each nursery school child with one in the non-nursery school group who had a birthday within six months of his. For both groups, the amount of association with other children in the family and other groups such as Sunday school seemed similar.

*Methods.*—After study of literature concerning colds, a list of symptoms indicating the presence of upper respiratory infection was constructed. This list was then revised and all medical terms changed to their lay equivalents. Care was taken to use terms in common usage and to reduce the list as far as possible but to maintain a detailed report of the cold.

To further validate the symptom check list, three physicians in active practice locally were interviewed. All were in agreement as to the terms used, that the list would give a detailed report of colds and that red, watery eyes, nasal discharge, mild loss of appetite, restless sleep, and headache are symptomatic of a cold. Two physicians also considered conduct changes such as irritability, listlessness, and rather inactive play as an important part of the diagnosis, particularly when endeavoring to differentiate infectious rhinitis from that of allergic origin. To be assured of the list's practicability in use, three mothers used it when their children had colds. All agreed that the list was understandable and easy to use. The symptom check list was then considered ready for use. The items included are listed in Fig. 3.



The mothers of every child were interviewed personally. Information was secured by the use of a questionnaire. All of the mothers of those two groups expressed interest and cooperated willingly in the study. The mothers were asked to keep a record of the number and severity of the child's colds by using the symptom check list for a period of ten weeks, Jan. 28, 1946, to April 8, 1946. At least once during this time each mother was contacted by telephone or personally; this served as a reminder of the study. At the close of the ten-week period the symptom check lists were collected by mail or personally through a home visit.

## RESULTS

### *Prevalence of Colds in Relation to Certain Variables.—*

1. *Prevalence of cold in relation to nursery school attendance:* The individual child's total cold score was obtained by adding all the symptoms that were checked during the ten-week period. This score served as a measure of the cold to be related to different variables. Table I shows the comparative total cold scores for the twenty-five nursery school children and the twenty-six non-nursery school children.

TABLE I. COMPARISON OF TOTAL COLD SCORES OF NURSERY SCHOOL AND NON-NURSERY SCHOOL CHILDREN, JAN. 28—APRIL 8, 1946 (TOTAL COLD SCORE = TOTAL NUMBER OF SYMPTOMS)

	RANGE	MEAN	STANDARD DEVIATION	MEDIAN	QUARTILE 3	COMPOSITE T-SCORE
Nursery school, N = 25	0-168	38.7	42.6	38	43.5	50.2
Non-nursery school, N = 26	0-123	37.3	32.86	20	59.3	49.2
Total N = 51	0-168	38.0	33.0	24.4	57.6	49.7

A few scores in each group were at the extreme ends of the distribution. Lindquist<sup>7</sup> says these scores receive an automatic weighting in proportion to the size of the standard deviation when the mean is taken. The composite T-score was used as a means of comparison because it removes this weighing. Lindquist defines the T-score as an arbitrary scale with a mean of 50 and a standard deviation of 10. The non-nursery school group had several low total cold scores shown by a median of 20 but quartile 3 of the distribution is 59.3, which shows a wide scatter. The mean difference is 1.4. As chance alone would account for a difference of this size 22.4 times out of 100, it cannot be said that the non-nursery school children had fewer or less colds than the nursery school children. The difference between the composite T-scores, 50.2 and 49.2, was slight. No significant difference existed between the two groups in the total number of cold symptoms in this ten-week period.

Fig. 1 shows the number of colds that each group had during the time of the study. Sixteen children in each group had one cold or more during the study. Seven of the nursery school group and ten of the non-nursery school group had two or three colds during the time of the study. Two of the nursery

school children had four colds during the study but none of the non-nursery school group had four colds during the ten-week period. The nursery school group averaged 1.5 colds and the non-nursery school group 1.3 colds during the study; the T-score device revealed no significant difference between the two groups in the number of colds.

Number of  
Children

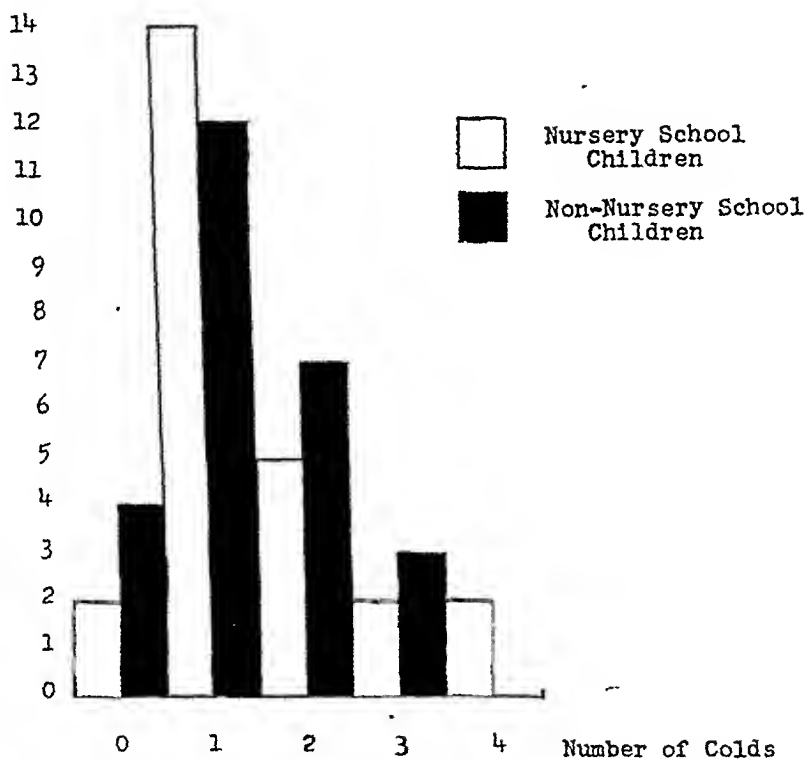


Fig. 1.—Comparison of the number of colds of nursery school and non-nursery school children, Jan. 28 to April 8, 1946.

To consider the severity of each cold, the total cold score of each child was divided by the number of colds he had during the time of the study. Table II shows a comparison of the severity of colds between nursery school and non-nursery school children. The nursery school children had an average cold score of 20.5 for each cold per child. The non-nursery school group showed an average cold score of 24.1 for each cold per child. The T-score was utilized to remove the automatic weighting of the scores at the extreme ends of the distribution. The composite T-score of 49.2 for the nursery school children and of 50.7 for the non-nursery school children shows a difference too slight to be

significant, as it would occur 51.6 in 100 by chance alone. Severity of colds was similar in the two groups.

TABLE II. COMPARISON OF SEVERITY OF EACH COLD OF NURSERY SCHOOL AND NON-NURSERY SCHOOL CHILDREN, JAN. 28—APRIL 8, 1946  
(AVERAGE COLD SCORE FOR EACH CHILD)

	RANGE	MEAN	STANDARD DEVIATION	MEDIAN	QUANTILE 3	COMPOSITE T-SCORE
Nursery school N = 25	0-74	20.5	16.3	15	24.75	49.2
Non-nursery school N = 26	0-123	24.1	24.1	18	25.0	50.7
Total N = 51	0-123	22.4	21.5	15.7	25.0	50.5

2. *Prevalence of colds in relation to age:* To determine the relationship of age and prevalence of colds, the children were considered as one group of fifty-one subjects. There were six children in the combined groups who had no colds during the time of the study. The children were grouped in age ranges of one year. Table III shows the prevalence of colds in relation to age. Children ranging from 23 to 35 months in age comprised 25 per cent of the total group; they included 24 per cent of the total number of children who had colds and had 25 per cent of all the colds suffered by the total group. Similar per cents at this age level and the other two of the one-year age grouping indicate similarity in the prevalence of colds at the various age levels of pre-school children.

TABLE III. PREVALENCE OF COLDS IN RELATION TO AGE, JAN. 28—APRIL 8, 1946

AGE OF CHILDREN IN MONTHS	NUMBER OF CHILDREN N = 51	PERCENTAGE OF TOTAL GROUP OF CHILDREN N = 51	PERCENTAGE OF TOTAL GROUP WHO HAD COLDS N = 45	PERCENTAGE OF ALL COLDS IN TOTAL GROUP N = 73	PERCENTAGE OF TOTAL GROUP WHO HAD NO COLDS N = 6
48 to 59	11	22	24	18	0
36 to 47	27	53	51	57	5.4
23 to 35	13	25	24	25	2.6

3. *Prevalence of colds in relation to the number of people living in the home:* The nursery school children and the non-nursery school children were grouped according to the number of people living in the home and the number of colds suffered during the study. Information regarding this variable is included in Table IV. Children living with two or three people at home in addi-

TABLE IV. PREVALENCE OF COLDS IN RELATION TO THE NUMBER OF PEOPLE LIVING IN THE HOME, JAN. 28—APRIL 8, 1946

NUMBER OF PEOPLE LIVING IN THE HOME	NUMBER OF CHILDREN			MEAN NUMBER OF COLDS PER CHILD		
	NURSERY	NON- NURSERY	TOTAL	NURSERY	NON- NURSERY	TOTAL
7-12	1	2	3	0	1.0	1.0
6	5	3	8	2.0	1.0	1.5
5	3	7	10	1.0	1.6	1.3
4	5	7	12	0.8	1.6	1.2
3	11	7	18	1.8	1.4	1.6

tion to themselves averaged 1.6 or 1.2 colds during the study. The children with four or five people in the home other than themselves averaged 1.3 or 1.5 colds during the study. Children with six to eleven people living at home in addition to themselves averaged 1.0 cold during the study. The mean number of colds varied only from 1.0 to 1.6. The differences are neither wide enough nor consistent enough to show significant relationship between the prevalence of colds and the number of people living in the home.

4. *Prevalence of colds in relation to diet:* Numerical diet ratings derived from the scale of Chaney and Ahlborn<sup>4</sup> were used to compare nursery school and non-nursery school children. To equalize the weighting given to individual scores when averaging a distribution, the T-score was again utilized. Table V shows the comparison of diet ratings of the nursery school and non-nursery school groups. The nursery school children had a mean diet rating of 83.4 and the non-nursery school children a mean diet rating of 77.5. The difference between the means is 5.9. As a difference of this size would occur by chance only three times in 100, it is considered to be a reliable one with something beside chance in operation. Furthermore, the composite T-score for the nursery school group was 52.2, whereas that for the non-nursery school group was 46.8. Diet scores of the nursery school children were significantly higher than those of the non-nursery school children.

TABLE V. COMPARISON OF DIET RATINGS OF NURSERY SCHOOL AND NON-NURSERY SCHOOL CHILDREN, JAN. 28-APRIL 8, 1946

	RANGE	MEAN	STANDARD DEVIATION	MEDIAN	QUARTILE 3	COMPOSITE T-SCORE
Nursery school N = 25	60-97	83.4	8.7	84.5	88.1	52.2
Non-nursery school N = 26	55-90	77.5	8.3	79.7	83.6	46.8
Total N = 51	55-97	80.3	8.5	82.2	86.1	49.4

Using the Pearson product-moment method of correlation, the relationship between the diet rating and the total cold score (total number of symptoms shown) was determined for the total group of nursery school and non-nursery school children. The coefficient of correlation was  $-.11 \pm .09$ , which shows no significant relationship between diet rating of these subjects and total cold score. All but two of the diet ratings showed adequate nutrition.

5. *Prevalence of colds in relation to weather:* To determine possible relationship between the prevalence of the common cold and weather, the ten weeks of the study were divided into two-week intervals and the number of colds occurring in each interval tabulated. The records of the temperature and humidity for Jan. 28 through April 7, 1946, were obtained from the weather station of Purdue University. In correlating temperature and the prevalence of colds the coefficient *epsilon* was calculated and found to be .52-.02. The coefficient *epsilon* was used because Peters and Van Voorhis<sup>5</sup> say of it, "*epsilon* has a standard meaning, free from bias and independent of the size of

the sample and of the number of classes into which the sample is divided." The correlation obtained (.52) is larger than the one significant at the one per cent level. Therefore, it is highly probable that there is some relationship between temperature and the prevalence of the common cold. This relationship is shown in Fig. 2. As temperature increased, the number of colds decreased. The relation of humidity to colds was not distinct.

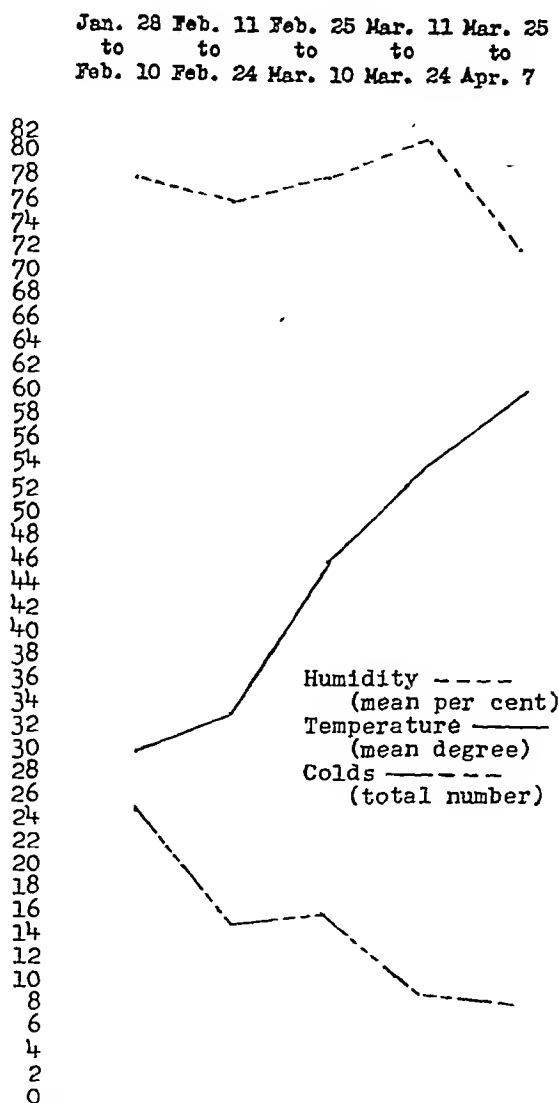


Fig. 2.—Relation of weather to the common cold (for seventy-three of fifty-one children, Jan. 28 to April 8, 1946.)

#### *Most Frequent Symptoms of Colds in Children of Pre-School Age.—*

Fig. 3 reveals the most frequent symptoms of colds in children of pre-school age who were included in this study. It shows that a pre-school child

with a cold had either a thin or thick nasal discharge, a mild cough, mild loss of appetite, and red, watery eyes; he was inclined to be irritable and chose rather inactive play. These symptoms which appeared are in basic agreement with those listed by the three physicians, whose opinions were sought in constructing a symptom check list as symptomatic of colds.

	1-40	41-80	81-120	121-160	161-200	201-240
Color:						
pale						
yellow						
blue						
flushed						
Skin:						
rash						
irritated						
Breathing:						
fast						
noisy						
difficult-very						
slightly						
Eyes:						
red						
watery						
Nose:						
discharge-watery						
thick						
contains pus						
Throat:						
red						
appears swollen						
drainage						
sore (child's report)						
Temperature:						
Loss of appetite:						
mild						
severe						
Hanson:						
(child's report)						
Vomiting:						
Headache:						
(child's report)						
Cough:						
mild						
severe						
Sleep:						
restless						
broken						
Irritable:						
Complaining:						
Indolent:						
Ornery:						
Type of play:						
none						
rather inactive						
Time in bed:						
Doctor called:						

Fig. 3.—Frequency of cold symptoms (In seventy-three colds of fifty-one children, Jan. 28 to April 8, 1946).

*Comparison of Colds in Same Child.—*

In 1947 nine of the children who were previously studied as members of the non-nursery school group entered nursery school. For these nine it was possible to compare the number and length of colds of the same child when he was not attending nursery school and when he was in attendance. Table VI shows this comparison for nine children.

TABLE VI. COMPARISON OF COLDS IN SAME CHILD NOT ATTENDING NURSERY SCHOOL AND ATTENDING NURSERY SCHOOL

INDIVIDUAL CHILD	JAN. 28-APRIL 8, 1946 NOT ATTENDING NURSERY SCHOOL		JAN. 28-APRIL 8, 1947 ATTENDING NURSERY SCHOOL	
	NO. COLDS	TOTAL NO. DAYS OF COLDS	NO. COLDS	TOTAL NO. DAYS OF COLDS
D. T.	3	15	0	0
A. A.	1	4	2	3
D. S.	1	2	0	0
J. D.	0	0	1	4
B. K.	1	14	2	25*
C. R.	1	5	1	10
M. K.	2	15*	2	11*
K. T.	3	21	2	6†
B. R.	2	12	1	3
Total	14	88	11	62
Average	1.55	6.28	1.22	5.63

\*Cold complicated by ear infection.

†Tonsils and adenoids removed Feb. 18, 1947.

These children averaged 1.55 colds while not in attendance at nursery school and 1.2 colds one year later when attending nursery school during the period from January 28 to April 8. There was no reliable difference in the number and the length of colds of the same children when not attending nursery school and when attending. While nine cases are not enough to form a definite conclusion, the figures in Table VI offer further evidence that daily exposure of healthy children to a group that is given adequate health protection does not cause any increase in colds.

#### CONCLUSIONS

Subjects of this study were fifty-one children between the ages of 23 months and 56 months. All children were above average in health status and from homes above the average socioeconomic level. Twenty-five were attending nursery school and twenty-six were not. The nursery school attended had a positive health policy and endeavored to keep sources of infection at a minimum. The ten-week record of the number and severity of colds was from Jan. 28 to April 8, 1946. The record provided the following findings concerning the prevalence of colds in the children studied.

1. There was no statistically reliable difference in the number and severity of colds suffered by children who attended nursery school and those who did not.
2. Various pre-school age levels showed similarity in the prevalence of colds.
3. No relationship appeared between the prevalence of colds and the number of people living in the home.

4. Children attending nursery school had a significantly higher diet rating than those who did not attend nursery school; both groups had adequate or superior diet ratings. There was no relationship between diet rating and prevalence of colds.

5. Colds decreased in prevalence as the temperature grew warmer. The relation of humidity to the prevalence of colds was not distinct.

6. The most frequent symptoms of a cold were: thin or thick nasal discharge, mild cough, mild loss of appetite, irritability, and rather inactive play.

7. Nine children who were studied as members of the non-nursery school group in 1946 attended nursery school the following year. They had no more colds while attending nursery school than when not attending.

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## PULMONARY EMBOLISM IN CHILDHOOD

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IN THE last decade, with advances in the knowledge of antieoagulants and antibiotics, widespread attention has been accorded pulmonary embolism in the adult. Little emphasis has been placed on this condition in children; in fact, it has been generally regarded as very rare.

This study deals solely with pulmonary embolism occurring before the age of 15 years. Pulmonary thrombosis, a related disease usually associated with infection, especially measles, is excluded.

### REVIEW OF THE LITERATURE

Among earliest reports of pulmonary embolism in childhood is that of Lösehn<sup>1</sup> in 1861. He described the case of a 9-year-old boy with a three-day illness characterized by pain and edema in the left leg and delirium. At necropsy there was thrombosis of the left femoral, popliteal, and anterior tibial veins. Death was caused by pulmonary embolism arising from this source. It was believed that phlebitis followed trauma, and, in turn, initiated thrombosis.

A similar case was reported by Curtin<sup>2</sup> in 1878. A 2-year-old child developed severe pain on the inner side of the right leg just below the knee twenty-hours after a fall. The leg became greatly swollen and discolored; the foot was everted. Death occurred three days later. At necropsy the vein at the site of injury was occluded by blood clot. Multiple emboli produced numerous infarcts in the lungs, some fresh, others the seat of necrosis.

Péhu and Horand<sup>3</sup> described an instance of embolism in a 6-year-old boy following otitis media, complicated by mastoiditis and suppurative thrombophlebitis of the right lateral and occipital sinuses and the internal jugular vein. Suppurative pulmonary infarcts were caused by septic emboli from the jugular vein. Guillemot's report<sup>4</sup> was of a similar case in an infant 7 months of age.

In an autopsy analysis Rupp<sup>5</sup> listed eleven instances of fatal pulmonary embolism under the age of 10, and seventeen between the ages of 10 and 20 years. Of these, three cases occurred at 1 year, five at 2 years, and three at 9 years. Little specific information was given regarding the cause of embolism in these children; all followed a severe exhausting illness with involvement of the heart, lungs, or kidneys.

Another case was described by Wessén<sup>6</sup> in a 4-year-old boy following a rib resection for empyema. Six days after operation the patient died suddenly while drinking milk. At autopsy there was a large embolus at the bifurcation of the left pulmonary artery extending into the middle lobe; the pulmonary trunk was free from embolus. The site of the original thrombus was not located, although the iliac arteries and the inferior vena cava were searched; an origin from the right side of the heart was considered.

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There was an additional case<sup>7</sup> in a 9-year-old boy following rheumatic carditis. The right atrium contained a large, firmly attached clot which extended into the pulmonary artery; the lower lobe of the right lung was infarcted. Of interest was the fact that the child was apparently well until twelve hours before death.

Two instances of fatal pulmonary embolism were reported by Fleischman,<sup>8</sup> both associated with measles. The first was in a 4-year-old girl who died suddenly due to a massive embolus which occluded the pulmonary trunk just above the valve and filled the left pulmonary, as well as part of the right pulmonary artery. Phlebothrombosis was discovered in the femoral and iliac veins. The second case was that of a one-year-old boy who also died suddenly while afflicted with measles. An embolus originating in a thrombosed superior sagittal sinus, was found in the pulmonary trunk.

Stulik and Rust<sup>9</sup> cited a case of fatal pulmonary embolism in a girl aged 11 months, who, for about two weeks prior to death, had had severe diarrhea and vomiting associated with fever. Five hours before death the child showed evidence of severe shock and developed the signs of consolidation in the right lung. At autopsy it was learned that both right and left pulmonary arteries were occluded, as were some of the smaller radicles. The origin of the emboli was not determined but was assumed to be in the veins of the lower extremities.

In another report<sup>10</sup> a female infant 7 months old, following pneumonia at 3 months of age, developed otitis media complicated by mastoiditis. On the eighth postoperative day the infant suddenly became cyanotic with rapid respiration and soon expired. At necropsy organized blood clot occluded the branches of the right pulmonary artery leading to the lower and middle lobes; the latter were collapsed. It was assumed that the emboli arose in thrombosed cranial sinuses.

Two additional cases were presented by Hosoi.<sup>11</sup> The first occurred in a boy aged 8 years with hemolytic staphylococcus septicemia. Multiple septic infarcts of the lungs and septic lesions of the heart and brain were caused by bacterial emboli originating in the sphenoidal and ethmoidal cells. The other case was that of a 6½-year-old girl who developed an abscess following appendectomy for a ruptured appendix. A massive pulmonary embolus caused death; thrombi were found in many subperitoneal veins.

Another case of embolism<sup>12</sup> was that of a 10-year-old boy who fell from a wall, injuring his arm. Vomiting and drowsiness appeared shortly after the injury and recurred intermittently until the time of death, two days later. At necropsy there was a pulmonary infarct occupying the entire right middle lobe. A clot was found blocking the main artery to the affected lobe. The right ventricle contained a pale, firm thrombus attached to the wall.

In an autopsy analysis Prettin<sup>13</sup> listed three cases of fatal pulmonary embolism. These occurred in a 3-year-old girl as a result of "heart failure," and in a 12-year-old boy and a 12-year-old girl following diphtheria.

An unusual case<sup>14</sup> was that of a 21-day-old infant who had been ill only three days with mild fever, dyspnea, cyanosis, and restlessness. The heart was the seat of a congenital anomaly consisting of transposition of the great vessels

and auricular septal defects, as well as of a valvular endocarditis. Small, easily detached thrombi were present on the free margin of the mitral leaflets. Masses of thrombi from this site were found in the pulmonary artery, causing infarction of the azygos lobe of the right lung.

Zuschlag<sup>15</sup> in 1947 presented an analysis of thirty-eight cases of infarction of the lung in children, due either to pulmonary thrombosis or embolism. It was thought that emboli caused infarction of the lung more frequently than pulmonary thrombosis. Data regarding individual cases, however, were not provided.

Most recently Crutcher and Daniel,<sup>16</sup> in an autopsy analysis, listed the case of a one-year-old boy with chronic bacillary dysentery associated with marasmus and anemia. Death was caused by a massive pulmonary embolus, the origin of which was not discovered.

#### CASE REPORT

*Clinical History.*—A 9-year-old boy was noticed to be unusually inactive on his birthday (July 24, 1947). In the morning he complained of pain about the left shoulder and in the lower half of the left side of the chest. No fever was noted and his appetite remained good. After an uneventful birthday party the child entered an auto preparatory to going for a ride. When the father arrived he found the child dead.

Subsequently it was learned that the boy had entered the hospital in December, 1946, seven and one-half months previously, because of cough, vomiting, and fever. On the day before this admission the boy became ill while at school; he began to cough, vomited once, and it was noticed that he had a fever. He was found later lying beside the highway, apparently having fainted on the way home from school. The past history was not remarkable.

On admission the child was flushed, febrile, and obviously ill. The eyes were red and watery. Respiration was rapid (35), deep, and labored. Slight redness was noticed about the external nares, and the ala nasae were seen to flare on inspiration. Examination of the heart revealed only a tachycardia (100). No abnormalities were detected in the lungs. In the abdomen slight tenderness was elicited in the right lower quadrant; there were no masses and no rigidity. The extremities were not unusual. There was no evidence of trauma. The temperature was 100.4° F.

X-ray examination of the chest on admission showed a slight increase in the hilus markings of the lungs, but no definite evidence of pneumonia. The white cell count was 32,600 with 73 per cent neutrophils. Urinalyses were repeatedly normal. A diagnosis of bronchopneumonia was considered, and penicillin and sulfa therapy were instituted.

In the following week cough became more troublesome and abdominal pain and tenderness more marked. It was noticed that the patient complained of pain on extension and lateral rotation of the right thigh. Another x-ray film of the chest taken on the seventh day was unchanged. The temperature remained elevated (101° F.), as did the pulse rate (110). The white blood count now was 12,500 with 69 per cent neutrophils. On the ninth hospital day the abdominal pain was maximum and was most pronounced over the middle of the right inguinal ligament. In this area also marked prominence of the superficial veins are noted. X-ray films of the pelvis, the upper two-thirds of both femurs, the abdomen, and the lumbar spine failed to reveal any abnormality. By the sixteenth day the findings in the right leg disappeared. About this time, however, the left leg similarly had become painful on movement, and was kept in a position of flexion.

The boy gradually improved under penicillin and streptomycin therapy. He was sent home on the twenty-seventh day with a guarded prognosis although he was feeling well. A final diagnosis was not made, although appendicitis, pelvic osteomyelitis, and retroperitoneal infection had been considered.

Five and one-half months after discharge, in May, 1947 (two months antemortem), the child again became ill. An x-ray film showed consolidation of the lower lobe of the

right lung. Mild pneumonia with pleurisy was diagnosed. The boy appeared to recover rapidly, however, and seemed well until the day of death.

*Postmortem Examination.*—At autopsy done fifteen hours later, external examination revealed cyanosis of the face as well as marked dilatation of the superficial veins of both thighs and the lower abdomen, especially on the right side. The left thigh was found to be one centimeter greater in circumference than the right. The left leg was externally rotated.

There were 100 c.c. of straw-colored fluid in the left, and 25 c.c. in the right pleural cavity. Striking changes were seen in the lungs. At the apex of the left lung (200 grams) there was a small, moderately firm, hemorrhagic area with a dull pleural surface. A similar but smaller fresh infarct was found in the lower lobe. At the base of the lower lobe of the right lung (170 grams) there was a thick superficial zone of scarring representing an older infarct.

At the root of the pulmonary artery the valve opening was obstructed by a massive embolus, 2.5 cm. long and up to 1.8 cm. in diameter. Similar embolic material was found adherent to the wall of the left pulmonary artery. Well-impacted embolus was present also in the small branches in both upper and lower lobes of the left lung. The friable character of the gray emboli suggested origin from an old, well-organized thrombus.

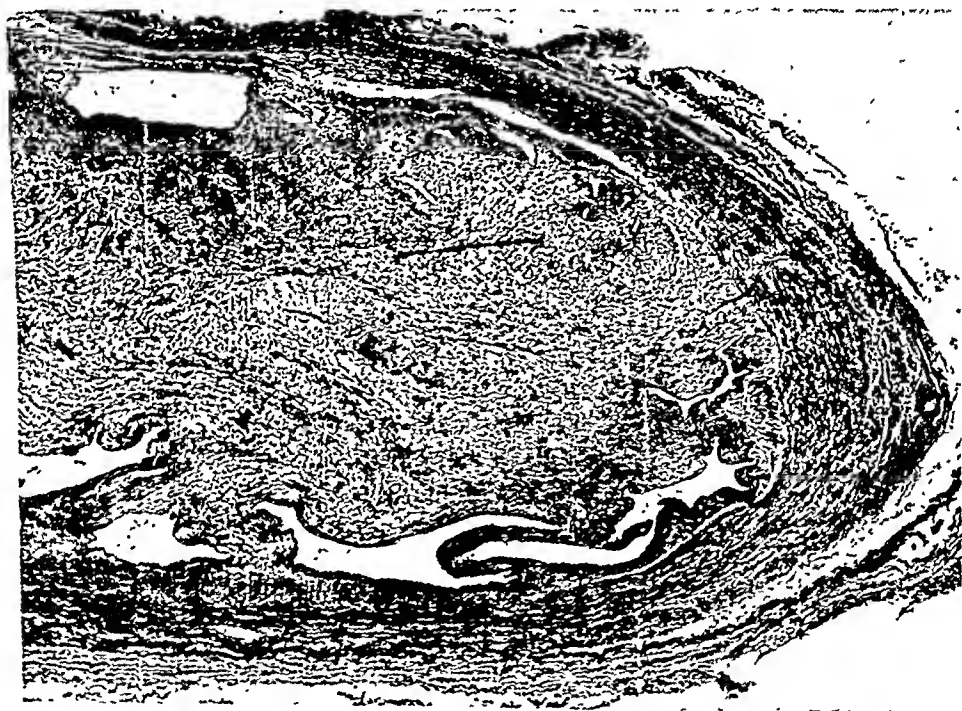


Fig 1—Photomicrograph of iliac vein showing striking reduction of lumen by completely organized thrombus ( $\times 30$ ).

The source of the emboli was found in the femoral and iliac veins and the inferior vena cava. Spongy yellow thrombus filled the right common iliac vein, and extended into the adjacent portion of the inferior vena cava, the intima of which was considerably roughened. Both external iliac veins and the adjacent portion of the femoral veins were almost completely occluded by confluent bands of connective tissue representing organized thrombus.

Acute dilatation was the only remarkable feature in the heart. In the abdomen there was acute passive congestion of all viscera.

Microscopic examination confirmed the gross findings. The infarcts of the left lung were found to be quite recent; the alveolar walls were still recognizable within the extensive

hemorrhage. The infarct on the right side was considerably older; the alveolar walls were necrotic, and most of the alveoli were partly obliterated by connective tissue.

The material in the left pulmonary artery was firmly attached to the wall by granulation tissue; its composition of vascular collagenous tissue indicated that it antedated the massive embolus at the pulmonary valve. The latter showed no evidence of organization. A section of the iliac vein (Fig. 1) showed the lumen to be replaced almost completely by organized thrombus that was intimately attached to the wall. This thrombus was composed of numerous small blood spaces separated by dense, poorly cellular, collagenous tissue containing many large mononucleated cells laden with hemosiderin. Sections of other organs were not remarkable except for acute passive congestion.

### COMMENT

The autopsy findings demonstrated conclusively that the sudden death of the 9-year-old boy was due to massive pulmonary embolism, the embolus arising in partially organized thrombus in the inferior vena cava and the common iliac veins.

The signs and symptoms during hospitalization seven and one-half months before death were undoubtedly those of bilateral thrombophlebitis of the lower extremities. This was indicated by the presence within the femoral and iliac veins of newly formed, fibrous, intraluminal intrusions of thrombotic origin. The cause of the phlebitis was obscure. While it may be postulated that the pulmonary symptoms at that time were those of pneumonia, the thrombophlebitis occurring as a sequel, the possibility of a spontaneous phlebitis cannot be disregarded. There was no history of trauma and the diagnosis of pneumonia was never definitely proved.

The episode of right-sided "pneumonia and pleurisy" two months before death, was the result of minor pulmonary embolism. This was demonstrated by the finding of a healing infarct in the lower lobe of the right lung. The several small, fresh infarcts in the left lung would appear to have occurred early on the day of death.

There would seem to be no doubt that thrombosis developed in the inferior vena cava following the bout of thrombophlebitis of the iliac and femoral veins. From this new site came both the preliminary small emboli and the final massive embolus.

TABLE I. NECROPSY INCIDENCE OF PULMONARY EMBOLISM, WITH SPECIAL REFERENCE TO EARLY AGE DISTRIBUTION

AUTHOR	NO. AUTOPSIES	CASES OF FATAL EMBOLISM		
		ALL AGES	0-9 YR.	10-19 YR.
Rupp <sup>5</sup>	13,000	657	11	17
Hosoi <sup>11</sup>	810	64	2	1
Prettin <sup>13</sup>	2,897	231	1	4
Crutcher and Daniel <sup>16</sup>	2,580	55	1	2
McCartney <sup>17</sup>	9,275	73	0	0
Rosenthal <sup>18</sup>	1,000	2	0	0
Belt <sup>19</sup>	567	56	0	0
Kirshbaum and Shively <sup>20</sup>	10,650	25	0	1
Hunter <sup>21</sup>	351	11	0	0
Neuhof and Klein <sup>22</sup>	5,146	88	0	0
Stevenson and Stevenson	466	20	1	0
Total	46,742	1,282	16	25

## DISCUSSION

Composite of several autopsy studies reveals that pulmonary embolism in children and young adults, while not common, occurs more frequently than is generally believed. The available necropsy surveys concerning embolism at all ages are summarized in Table I. Of a total of 1,282 cases of fatal embolism encountered in 46,742 routine autopsies, there were sixteen instances, or 1.25 per cent, in the 0- to 9-year group, and twenty-five, or 1.95 per cent, in the 10- to 19-year group. It must be emphasized that these results represent only the necropsy incidence of pulmonary embolism. The percentage of autopsies in the age groups represented by these cases remains unknown.

*Etiology.*—Pulmonary embolism in children is confined almost entirely to the nonoperative group. In only two of the thirty summarized cases is embolism known to have followed operation; in both it was thought that preceding infection played the primary role in producing the pre-embolic thrombosis. Infectious disease, generally of an acute variety, antedated embolism in fifteen cases, while chronic debilitating disease, presumably not associated with acute infection, was the basis for embolism in twelve. Trauma was the apparent precipitating factor in only three cases. The primary diseases complicated by embolism are listed below; those of an obscure or doubtful nature are not included.

Diseases complicated by pulmonary embolism included otitis media and mastoiditis, 3; measles, 2; diphtheria, 2; pleural empyema, 1; appendiceal abscess, 1; rheumatic carditis, 1; bacterial endocarditis, 1; bacillary dysentery, 1; septicemia, 1; pneumonia, 1.

The origin of emboli in the infectious group was found in both the systemic circulation and in the heart. Emboli originated in the heart in two cases; both were associated with endocarditis. Thrombophlebitis of the extremities provided the source in three cases and retroperitoneal phlebitis was the cause in another. The source of emboli in five cases, within thrombosed intracranial sinuses, associated either with local or general infection, must be assumed to be a feature peculiar to childhood. The embolic source was not determined in five instances.

It is difficult to assay the role of sex in the causation of pulmonary embolism. Emboli were found in nine boys and six girls; in some cases, however, the sex of the child was not stated.

*Pathologic Anatomy.*—Only sixteen of the thirty reports of pulmonary embolism provide complete necropsy data. Embolism resulted in infarction in eight cases; of these, the right lung alone was involved in three, and both lungs were affected in five instances. Infarction failed to occur in seven cases. These results correspond closely to the size of the emboli; multiple small emboli were found in nine cases, while a single, massive embolus was discovered in seven instances. Although single infarction was not described in the left lung in any case, it is noteworthy that emboli lodged in the left, as frequently as they did the right pulmonary artery.

In adults thrombosis of the veins of the extremities, subsequent to disease elsewhere in the body, provides the major source of pulmonary emboli. In

Allen's series,<sup>23</sup> in which all age groups were included, 95 per cent of emboli arose in the deep veins of the legs. This is not the situation in children. Of the sixteen childhood cases described completely, thirteen children had thrombosis of the veins within or immediately adjacent areas of infection or trauma. The remaining three are the only known reported instances in children in which thrombosis of the veins occurred at a site unrelated to the primary disease. In the two cases of measles reported by Fleischman,<sup>8</sup> the cranial sinuses and the left femoral and iliac veins, respectively, were involved; the lesion in both was termed phlebothrombosis. In our case thrombophlebitis was present; it could not be determined whether this was primary or secondary.

In addition to these three instances, the only reference to thrombosis of the veins of the extremities in children is provided by Zuschlag,<sup>15</sup> who mentions involvement of the femoral vein in four instances and the iliac vein in an equal number. A search for thrombosis in the deep veins of the legs was performed by Hunter and collaborators<sup>21</sup> in 351 autopsies; it was found in 52.7 per cent of the patients, the youngest of whom was 15 years of age. In Barker's<sup>24</sup> study of primary idiopathic thrombophlebitis the youngest patient involved was 21 years old. Levinson<sup>25</sup> writes that he has encountered only two instances of peripheral thrombophlebitis in children, except for the transient variety following "cut-down" for intravenous therapy. One of his cases was in a 4-year-old child who had femoral thrombophlebitis associated with intestinal lymphosarcoma; the other was due to an infection of the thigh.

*Clinical Findings.*—The clinical aspect of pulmonary embolism in children is generally similar to that in adults. The majority of patients showed signs and symptoms which, either at the time of the illness or in retrospect, were those suggestive or typical of pulmonary embolism. Undoubtedly some cases were misdiagnosed because the possibility of embolism at an early age was not considered. The most remarkable feature is the frequency with which sudden death occurred. In seven of sixteen cases a single, massive embolus caused sudden death. The fatal embolus in some instances was preceded by smaller emboli, while in others it occurred as a solitary event. In Zuschlag's<sup>15</sup> series, sudden death occurred in 24.4 per cent of children having either pulmonary thrombosis or embolism.

#### SUMMARY

1. The literature concerning pulmonary embolism in children is reviewed and reference is made to twenty-nine previously reported cases.
2. A case of pulmonary embolism causing sudden death is reported in a 9-year-old boy; emboli arose in thrombosed veins of the extremities.
3. The clinical and pathologic features of childhood pulmonary embolism are discussed; the rarity of peripheral thrombophlebitis in children is emphasized.

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## DYSGERMINOMA OF THE OVARY IN A FOUR-YEAR-OLD GIRL WITH METASTASES CLINICALLY SIMULATING WILMS' TUMOR AND ADRENAL NEUROBLASTOMA

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DYSGERMINOMA ovarii has not been found listed in modern textbooks of pediatric medicine, surgery, radiology, or in pediatric journals. Nevertheless, in gynecologic and pathologic literature up to 1947, Mazel<sup>5</sup> found 250 cases, Moreton<sup>7</sup> over 300 cases, and Schneider and Vesell<sup>10</sup> more than 300 cases already reported.

Opinion is still divided in the literature in regard to the degree of malignancy, the incidence of bilateral ovarian dysgerminomas, and the nature and advisability of surgical and radiological treatment. In a previous paper on sympathoblastoma,<sup>4</sup> it was mentioned in the differential diagnosis of these adrenal and abdominal tumors. We are inclined to agree with Mazel,<sup>5</sup> that the neoplasm is usually highly malignant, that surgical management logically must be as radical as that of carcinoma of the ovaries, that the neoplasm attacks even the very young and surgeons are tempted to restrict themselves to conservative removal of the tumor and to rely on postoperative radiation, that once the diagnosis is made the most pressing objective is not conservation of potential procreative power but the preservation of life itself.

We have recently been called upon to give postoperative radiation to a 14-year-old girl riddled with metastases who had only removal of the ovarian dysgerminoma and its adjacent tube. The metastases appeared in less than one year after this conservative surgery and she died within six months of the appearance of the metastases. We cannot agree with repeated pleas for conservative surgery in spite of its occasional successes. Radical surgery with panhysterectomy and bilateral salpingo-oophorectomy seem imperative. If tumor remains we do not object, and in fact we favor postoperative radiation therapy to pelvis, periaortic nodes, thoracic duct, and supraclavicular areas similar to that accorded seminomas, but with it we do not expect or promise permanent cure. Moreover, if the possibility of residual tumor remains following radical surgery, we cannot agree with the reasoning that, "we customarily withhold postoperative irradiation because it will permanently sterilize and will prevent the full maturation of the individual. If malignant cells have been left in the operative field, x-rays will probably not destroy all of them; if neoplasm has not been left, x-ray treatment is superfluous and will bring on the detrimental effects of destruction of the remaining ovary." We would repeat Mazel's plea for the most radical surgery, and the most pressing objective is not the conservation of

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potential procreative power but the preservation of life itself. Until postoperative irradiation is given an opportunity following radical surgery, we will not know whether it can destroy the radiosensitive cells in the body sufficiently to preserve or even prolong life.

#### CASE REPORT

A Negro girl 4 years, 3 months old, was admitted to the hospital with a chief complaint of pain in the epigastrium, nausea, and vomiting of two days' duration. A mass the size of a small lemon was palpated in the left upper quadrant on Dec. 11, 1944, which within three days became the size of a grapefruit. There was a history of a cold in the head which started four weeks previously with sneezing and cough. One week later a purulent sore developed on the leg. The sore broke down and spread to the face, trunk, and extremities. A sulfanilamide ointment was applied with improvement, but at the time of the examination there was persistence of the infection on the skin of the right ear, apparently impetigo contagiosa.

The previous history showed that the father had syphilis four years previously and had received treatment for the disease. The mother had a negative blood Wassermann. The child was born at term, talked at 11 months, and walked at 15 months. The general health had been good until the beginning of the present illness. The patient appeared to have lost 10 to 15 pounds in weight. Beginning Dec. 11, 1944, the patient had been having fever with excessive sweating day and night. Three months before the present illness the patient was pinned under a heavy object which fell on her upper abdomen.

Physical examination showed a well-developed, lean girl of 4 years. There was generalized glandular enlargement with the cervical, axillary, inguinal, popliteal, epitrochlear, and supraclavicular nodes involved. The temperature was 100.2° F., pulse 130, and respirations 33.

The abdomen showed a visible bulge confined to the region above the navel. The mass was 9 by 13 cm., fixed, firm, did not fluctuate or pulsate, and appeared to be symmetrical in the midline, not attached to the abdominal wall. It was slightly tender and was mobile with respiration. The rest of the abdomen was flat. The liver and spleen were fully two finger-breadths below the costal margin. The kidneys were not felt.

Percussion revealed tympany on the left and dullness on the right but on the second hospital day this phenomenon seemed to have disappeared.

The laboratory data showed hemoglobin 44 per cent, red blood cells 2.54 million white blood cells 11,000, polymorphonuclears 63 per cent, eosinophiles 2 per cent, lymphocytes 24 per cent, mononuclears 10 per cent, immature cell 1 per cent. Repeated urine examination was negative. The blood Wassermann test was negative. The tuberculin 1:10,000 was negative. The blood smear showed a marked normocytic, normochromic anemia with variation in size and considerable regeneration, including a number of normoblasts. There was a shift to the left with moderate toxic changes and an occasional myelocyte. The platelets were reduced to about one-half normal, and there were a large number of atypical monocytes. The hematologist's impression read, "This is not a blood dyscrasia but apparently is a reaction to some rather severe condition, and inasmuch as there is enlargement of the spleen here, the things to think about along this line are malignancy, tuberculosis involving the spleen, Hodgkin's disease, although the platelet count is against this latter, and such other malignant conditions."

Röntgenogram of chest showed no pneumonia, tuberculosis, or other definite pathologic change. Abdominal film showed definite moderate enlargement of the liver which displaced the gas-filled colon downward at the hepatic flexure. The spleen and kidneys were not outlined and diaphragm was not unusual in position. Intravenous pyelograms showed satisfactory filling and function of the right kidney and right ureter and bladder filled with diodrast. The left kidney failed to concentrate diodrast and the conclusion was left kidney or adrenal tumor, probably Wilms' tumor. Deep roentgen therapy with dose of 200r was given anteriorly over the left kidney on Dec. 27, 1944.

Whole blood transfusion was given.

Of various clinical impressions, including Wilms' tumor of the left kidney, adrenal neuroblastoma, Hodgkin's disease, and lymphosarcoma, the physician most closely associated with the study of the case favored lymphosarcoma.

#### NECROPSY REPORT

The patient died Dec. 28, 1944, and necropsy was performed three hours and ten minutes after death. There was marked muscular atrophy and slight rigor mortis was present throughout. The eyes showed slight exophthalmos and sclerae had a slight yellowish tinge, the corneas were clear, pupils equal and regular in outline. The nose showed a small amount of hemorrhagic discharge from both nostrils. The mouth showed parched lips, and normal temporary teeth with purplish discoloration along the gingival margins. There was a large ecchymosis in the labial gingiva inferior to the lower incisors. The palatine tonsils were moderately hypertrophied and slightly hyperemic. The pharynx was moderately injected. The superficial and deep cervical nodes were enlarged, firm, and discrete. The thyroid gland, trachea, and cervical blood vessels were negative. The abdomen was level with the inferior costal margin, with a slight bulge in the upper left quadrant. A small, brownish-red, macular rash was scattered over the abdomen. The external genitalia were normal for a 4-year-old girl. The extremities showed no relevant lesions.

On section of the thorax, the thymus was normal in size and consistency. The left pleural cavity contained about 50 c.c. of hemorrhagic fluid, the right 35 c.c. of similar fluid. The esophagus was negative and the heart normal. The ascending aorta showed a few atheromatous plaques near the coronary arteries. The plaques were bright yellow in color. The lungs appeared normal with no macroscopic metastases found.

On opening the abdomen, the peritoneal cavity contained about 180 c.c. of hemorrhagic fluid. The mesentery showed numerous large ecchymoses, especially near the reflection over the transverse colon.

The liver extended 8 cm. below the inferior costal margin in the midline. There was a large mass in the region of the left kidney which extended from the right border of the spinal column to the left lateral abdominal wall. It was firm in consistency and irregular in outline. There were numerous adhesions between the fundus of the gall bladder and the adjacent serosal surfaces.

A large blood clot was found in the true pelvis. The serosal surfaces were smooth, moist, and glistening. The intestines showed no special lesions. The stomach showed a few small, petechial hemorrhages but the mucosa otherwise appeared normal. The gall bladder and bile ducts were normal. The venae cavae appeared normal.

The liver was normal in size and shape, firm in consistency, brownish red in color, mottled with sharply defined, pale yellow areas varying in size from 1 to 5 mm. in diameter. Sections showed the same type of mottling. The normal structure of the liver was easily discernible.

The spleen showed a few fibrous adhesions.

The pancreas was involved in the tumor mass from which it was dissected out only with difficulty.

The abdominal aorta was not remarkable.

The right adrenal gland appeared normal.

The right kidney measured 7.5 by 4.5 cm. and was firm in consistency. The capsule stripped with ease, revealing a pale, smooth, brownish yellow surface with a few large, punctate hemorrhages from 1 to 3 mm. in diameter. The cortex was normal in thickness and cortical markings were indistinct. The medulla and pelvis were normal. The ureter was normal.

The large mass on the left side arose from the left adrenal.

The left kidney measured 10 by 5.5 cm., was firm in consistency, and the capsule stripped with ease and revealed a pale, uniformly smooth, brownish yellow surface with a few punctate hemorrhages. The cortex was normal in thickness and cortical markings were indistinct. The configuration of the medullary pyramids was completely obliterated by a large, firm, brownish mass which almost completely flattened the pelvis and extended outward in finger-

like projections into the cortex. The corticomedullary junctions were irregular in configuration.

The mesenteric lymph nodes were markedly enlarged and matted together with the mass. Some were firm in consistency, while others were soft and appeared fluctuant. Sections showed white surfaces with irregular dark areas. Some of these hemorrhagic areas were small while others were the size of the entire lymph node. The fluctuant nodes had necrotic centers. The large mass in the region of the left adrenal was 10 by 7 by 6 cm. It was lobulated, irregular in contour, and some of the lobules were soft and fluctuant while others were firm. The mass was divided into lobules by fibrous tissue septa. The cut surface showed small, irregular, white areas within the dark red areas and many of the lobules had necrotic centers.

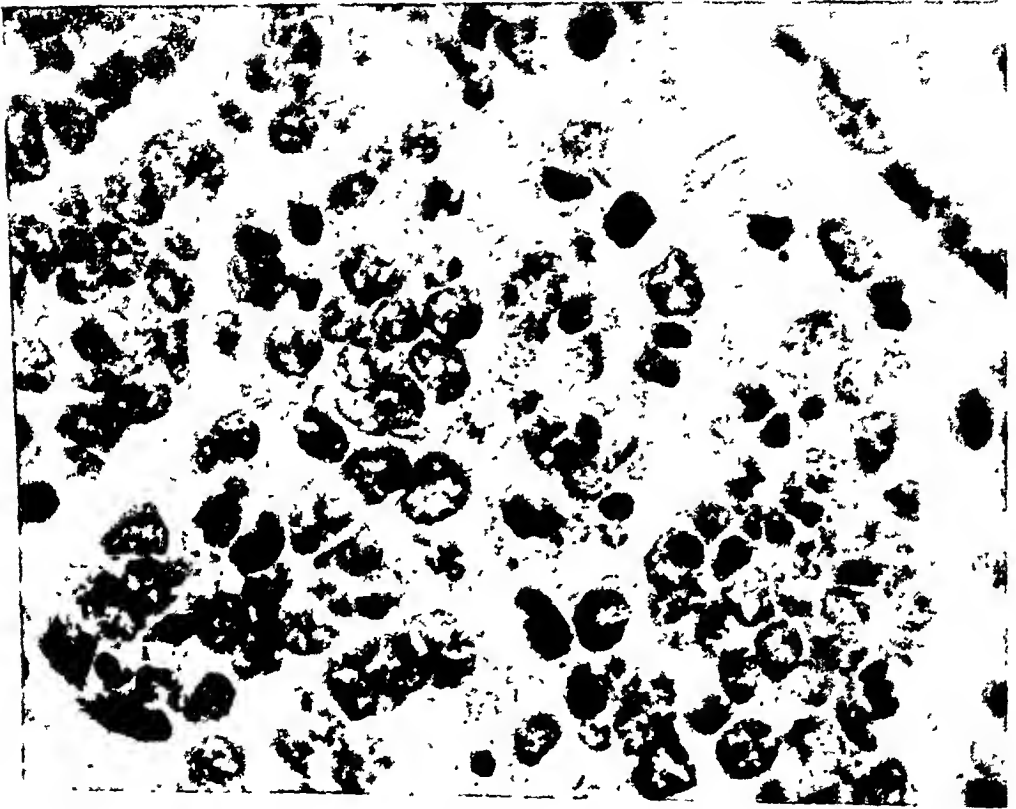


Fig 1—Dysgerminoma ovary. Hematoxylin and eosin stain ( $\times 800$ )

The spleen weighed 30 grams and was macroscopically normal.

The pancreas appeared pale and brownish yellow, with dark red markings in the interlobular septa. Sections showed a pale, brownish yellow surface with a light brown mass extending into the body in fingerlike projections.

The pelvic organs were removed en masse.

The bladder was normal and contained a small amount of straw colored urine.

The vagina, uterus, and tubes appeared normal for a 4 year old girl.

The right ovary measured 5 by 3 by 3 cm. The left ovary measured 4 by 2.5 by 3 cm. The external surfaces were purplish red and mottled, with sharply defined yellow areas of varying sizes. On the superior aspect of the left ovary there was a small cavity with necrotic borders. Sections showed a dark red surface with numerous sharply defined, brownish yellow areas

varying in size from 3 to 5 mm. in diameter. These nodules were firm in consistency and comprised the greater part of both ovaries. The blood clot found in the true pelvis appeared to originate from the ruptured left ovary.

Microscopic examination of the lungs disclosed tumor cells in the large vessels. The urinary bladder showed tumor cells in the serosa. The right adrenal showed nests of tumor cells in both the cortex and medulla. The left adrenal was completely replaced by the tumor, which contained prominent areas of necrosis and hemorrhage. The right kidney showed nothing unusual. The left kidney showed very extensive replacement by tumor tissue, with infiltration most marked in the medulla. Some of the glomerular tufts were invaded and almost replaced by tumor sheets, and tumor cells were also seen within many blood vessels. The pancreas showed patchy invasion by nests of tumor cells and a moderate amount of interstitial fibrosis. Lymph nodes had extensive tumor infiltration with prominent areas of necrosis and hemorrhage. In the pulp of the spleen, tumor cells were seen. Nodules of tumor metastases were found in the liver, some small and others confluent, and individual tumor cells were seen in the sinusoids. The ribs and sternum had tumor metastases in the bone marrow.

In the ovaries, the tumor cells had scanty, granular, and slightly acidophilic cytoplasm which surrounded large rounded or oval nuclei, each about 10 to 14 microns in the longest diameter. The nuclei were hyperchromatic with their chromatin material in coarse clumps. Mitotic figures were numerous. The growth was rich in blood supply and hemorrhage and necrosis were irregularly scattered throughout the tumor and the larger metastases. The slides were submitted to Dr. Emil Novak, Chairman of the Ovarian Tumor Registry, who confirmed the diagnosis of dysgerminoma of the ovary.

#### DISCUSSION

All recent publications on the histopathology of ovarian tumors agree on the description of the structure of dysgerminoma.<sup>6, 8, 9, 11</sup> Novak,<sup>8</sup> in particular, gave an excellent description. Seegar<sup>11</sup> described the tissue microscopically as suggesting the appearance of caviar. However, we have to bear in mind that this applies to the areas in which necrosis, hemorrhage, and other degenerative changes are not found.

It is interesting to note that both Chevassu<sup>2</sup> in 1906 and Chenot<sup>1</sup> in 1911 gave an excellent histologic account of the tumor.

Chevassu<sup>2</sup> in his section on anatomic pathology described "seminome" as a tumor whose cells are rounded and have voluminous ovoid nuclei and whose cytoplasm is markedly reduced. The nucleus is about 12 microns in its longest diameter and contains one, two, or three bright nucleoli. Around the nucleus there is a halo of clear cytoplasm. Peripheral to this halo the cytoplasm takes a deeper stain. He also stated that the cells are very delicate and alter very rapidly and for this reason he recommended very early fixation in Zenker's fluid. He went further to state that a similar picture is met with only in some ovarian tumors.

Chenot<sup>1</sup> in his thesis on "Epitheliomas Primitifs de l'Ovaire" with the assistance of his friend Masson on the histologic technique, arrived at a similar description as that of Chevassu.<sup>2</sup>

With regard to the histogenesis of the tumor, Chenot agreed with Chevassu that both "seminome" and dysgerminoma originated from the sex cell on condition that the sex cell be of "the indifferent type," that is, the sex cell before it differentiates into male or female sex cell. Furthermore, this definition was

written before the application of the hormone tests in the differential diagnosis of ovarian and testicular tumors was common knowledge. Moreover, Chevassu<sup>3</sup> in 1910, in his report on the prognosis of testicular tumors, showed statistically that this tumor gave a better prognosis following surgery than the other testicular tumors.

#### SUMMARY

In summary, we have reported a case of bilateral dysgerminoma in a 4-year-old Negro girl with rupture of the left ovary resulting in hemoperitoneum, with metastases into the following organs in the order of extent:

1. Left adrenal and left kidney.
2. Lymph nodes, (a) mesenteric (b) periaortic (c) cervical.
3. Pancreas.
4. Liver.
5. Right adrenal.
6. Serosa of urinary bladder and stomach.
7. Bone marrow of sternum and rib.

Vascular dissemination was observed in the following: (a) lungs, (b) left kidney, (c) liver, (d) spleen, (e) peripheral blood.

There was extreme emaciation and mild jaundice.

The early literature on the histogenesis of dysgerminoma and the various case reports found in young patients have been reviewed and presented.

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# PHENYLPYRUVIC OLIGOPHRENIA IN A JEWISH CHILD

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IN 1934 Fölling<sup>1</sup> described mental deficiency associated with phenylpyruvic acid in the urine, and so made another inroad into the large group of "primary" mental defectives. Since that time Jervis<sup>2</sup> has reported more than 200 cases of this disease. In contrast to the Tay-Sachs form of idiocy, not a single case was found in a Jewish person. There is a similarity between Tay-Sachs disease and phenylpyruvic oligophrenia in that both are associated with metabolic disorders, the former with a biochemical error involving lipids and the latter involving an amino acid. It is to be noted that a large proportion of Jervis' cases came from mental institutions draining large areas of Jewish population.

The cases to be presented here have the genetic distinction of being the first such cases reported in Jews.

## CASE REPORT

A. C. is a 6-year-old white boy, the first-born, whose parents at the time of his birth were 29 years old. The mother's pregnancy was normal and full-term, and labor was uneventful. The infant was bottle fed. Cereals were added at 3 months of age, and vegetables, fruits, eggs, meats, etc., were added in the succeeding months. Ten drops of oleum pereomorphum and orange juice in adequate quantities were begun at one month and continued until the present time. At the age of 2 weeks he was operated on for a strangulated inguinal hernia and made an uneventful recovery. His other illnesses included bilateral otitis media at one year and a respiratory infection with high fever at 3 years of age.

The mother noted that the infant's mental development was slow from early infancy. Although he walked at 19 months of age, he didn't say a word until he was 3 years old. He developed some bowel control at one year of age, but had frequent lapses. He developed daytime control of his bladder at 4½ years of age but still wet his bed at night. He never adjusted himself to other children, nor cooperated with them. He still appears afraid of them and always fights with them. He was admitted to one school at the age of 5½ years, but was so difficult to manage that his mother was requested to remove him. He was then placed in another school, where he was retained by means of rewards and punishment until he began to vomit. The vomiting gradually became worse and he was admitted to the Beth Israel Hospital as a possible surgical case. No organic cause for this vomiting was found, and it subsided without any specific therapy.

When the acute episode subsided, the following positive findings were noted: (1) a slim, dull-looking boy with fair complexion, blue eyes, and light brown

hair; (2) head circumference only 18 inches ( $2\frac{1}{2}$  inches less than normal); (3) auricles abnormally shaped; (4) right inguinal sear and atrophic right testicle.

The neurological examination revealed the following positive findings: (1) hyperactive deep reflexes; (2) halting type of gait; (3) diminution of associated hand swinging when walking; (4) hypotonia; (5) generalized muscular weakness.

Mentally he was a hyperactive, noisy, unkempt child. His speech was indistinct, his vocabulary was very limited. He showed little interest in the other children on the ward other than to beg for candy or toys. He was frequently incontinent of both urine and feces. On one occasion he was noted tasting his own stool; on another he was seen eating paper.

The positive laboratory findings were: (1) urine was persistently positive for phenylpyruvic acid; (2) the electroencephalogram showed slow waves of high voltage but no noticeable focal abnormalities; (3) the psychometrics showed an I.Q. of 34 on (a) the revised Stanford Benet, (b) the Cornell Coxe Performance Scale, and (c) the Goodenough Drawing Test.

The family history is contributory. The father showed phenylpyruvic acid in the two specimens of urine tested. His I.Q. as measured on the Bellevue-Wechsler test was found to be 69. He is a presser of gloves, works steadily, and earns about \$35.00 per week.

He is aware of his son's mental retardation, has expressed interest, and shown cooperation in the various tests done on the child.

The mother, as well as the younger sibling of this marriage, have a normal mentality and no phenylpyruvic acid in the urine. The parents are not blood relations, both born in different towns in Russia. They state that their genealogy shows all their ancestors have been Jews.

Penrose,<sup>4</sup> and particularly Jervis,<sup>3</sup> have presented careful and detailed studies on the genetics of this disease. The latter has postulated that it is transmitted by a rare recessive autosomal gene present in both parents who are heterozygous. The theoretical expectation in a marriage involving two heterozygotes is that 75 per cent of the siblings will be normal, and 25 per cent affected. In an analysis of 200 cases of phenylpyruvic oligophrenia, Jervis found that 42 per cent of the offspring of carriers of this disease were affected. However, correction of the raw percentage by special methods of statistical analysis reduced the figure to 25 per cent. These findings, therefore, seemed to confirm Jervis' theory of the inheritance of this disease. Consanguinity is an important factor in the incidence of this disease, which is more common in Norway than in England, more common in England than in the United States.

Jervis reported one instance where the mating of an affected individual with a normal individual resulted in four siblings, two affected and two normal. He put forward the hypothesis that the unaffected parent was heterozygous. He pointed out that although this was unlikely in the absence of consanguinity, it was not impossible when one considered that the percentage of heterozygotes or carriers was above 1 per cent.

The case presented in this paper is very similar genetically to the one just quoted from Jervis. Again one out of two siblings are affected and one must



postulate that the mother is a heterozygote if the method of inheritance is by a single autosomal recessive gene. However, the presence of two such cases cast some doubt as to the validity of this theory of inheritance in this disease.

Although the gene for phenylpyruvic oligophrenia is a recessive one, it is noted that the carriers, the heterozygotes, are predisposed to mental deterioration. It is, therefore, believed that the gene for phenylketonuria is not completely recessive. Inasmuch as carriers of the recessive gene are about 1 per cent of the population and the actual incidence of the disease is about 1:25,000, it is possible that many of the mentally ill are carriers of this gene.

It seems to us that the father of our patient was actually a *forme fruste* of phenylpyruvic oligophrenia. He showed phenylpyruvic acid in his urine and scored 69 on the Wechsler-Bellevue test. His neurological examination was within normal limits. Despite his borderline intelligence, he made a satisfactory and independent economic and social adjustment in a strongly competitive community such as New York City. Jervis reported two patients with this disease with psychometrics of 60, but neither showed as good a social adjustment as the patient just reported. It is not unlikely that further investigation will reveal other unsuspected "*forme fruste*" cases of phenylpyruvic oligophrenia.

The metabolic error in this disease is explained in the following way. Phenylalanine is converted to phenyllactic acid and phenylpyruvic acid or directly to tyrosine. The phenylpyruvic acid is then converted to tyrosine. In this disease the enzymes necessary for these conversions are deficient. Jervis and associates found that the blood of patients with phenylpyruvic oligophrenia contained unusually large amounts of phenylalanine but no phenylpyruvic acid nor phenyllactic acid, even after the latter two substances were administered. They concluded that the kidneys were able to deaminate phenylalanine although the extra renal tissues were unable to oxidize it. Penrose and Quastel found that the administration of alanine and tyrosine to phenylketonurics caused no change in the excretion of phenylpyruvic acid, whereas the ingestion of dl-phenylalanine, L-phenylalanine and d-phenylalanine led to an increased excretion of phenylpyruvic acid.<sup>10</sup>

Levine and collaborators<sup>8</sup> found that premature infants, when given high protein, as cow's milk, excrete in the urine excessive amounts of p-hydroxyphenylpyruvic and p-hydroxyphenyllactic acids. This disorder of premature infants was prevented by administration of ascorbic acid. It was possible to induce a similar condition in full-term infants by giving large amounts of phenylalanine or tyrosine and abolishing it again with extra ascorbic acid. Closs and Fölling<sup>9</sup> found small amounts of phenylpyruvic acid in the urine of rats with vitamin B<sub>1</sub> deficiency. They concluded that thiamine was implicated in the oxidation of phenylpyruvic acid.

Phenylpyruvic acid is never found in the urine of normal people, whereas phenylketonurics excrete from 0.5 to 3 Gm. daily.

Jervis tried to determine whether phenylpyruvic acid was toxic and interfered with growth and development. He, therefore, gave large quantities to one litter of kittens and used another litter as a control. No difference was noted in the two litters. On the other hand, no proof was found that the mental defect was the cause of the metabolic error.

*Diagnostic Features.*—The two cardinal features in the diagnosis of this disease are mental retardation, almost invariably of a severe grade, and the presence of phenylpyruvic acid in the urine. Other neurological findings commonly present are not diagnostic. The most prominent of these are muscular rigidity, alterations of posture and gait, tremors, and athetoid movements. It is also to be noted that these children are characteristically fair in complexion and not unattractive in appearance despite their low intelligence. Approximately, one-half of the cases reported showed skin lesions eczematous in nature.

*Therapeutics.*—Replacement therapy by the administration of phenylalanine or tyrosine has proved futile, for there is a deficiency of an oxidizing enzyme for the proper metabolism of phenylalanine or its deaminated derivatives, with failure of normal conversion to tyrosine. Administration of large doses of Vitamin C is similarly futile, as its oxidation action is on p-hydroxyphenylpyruvic acid, which is a deaminated derivative of tyrosine. Since in this form of idiocy there is a failure of conversion to tyrosine, ascorbic acid is useless as an oxidizing agent for phenylpyruvic acid. Attempts are now being made to test the efficacy of glutamic acid in this disease; this is a nonspecific method of approach, for this acid has been of value in increasing the metabolism of brain cells and raising the intelligence in other mental defective conditions.

#### SUMMARY

A case of mental deficiency with phenylpyruvic acid in the urine is reported in a Jewish child for the first time. Other neurological and psychiatric features were present. The father of this child presents a forme fruste of the disease. The genetics and metabolic error of this disease are briefly discussed.

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## AN OXYGEN-HUMIDITY-AEROSOL UNIT FOR INFANTS

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FOR many years the crop tent and steam kettle have been of recognized value in the treatment of laryngotracheobronchitis. More recently "cold steam" methods have removed the disadvantages of high temperature humidity. Such a method was developed in the Children's Hospital of Pittsburgh by Simpson,<sup>1</sup> utilizing a water sprayer or oxygen humidifier resembling the nozzle on a garden hose with a jet of oxygen to further break up the water droplets. This equipment has proved satisfactory over a period of four years and has been recently modified by the addition of an aerosol nebulizer, in order to broaden its clinical application. While the addition of aerosols to oxygen tents is not new<sup>2</sup> the modification described in this paper results in a compact unit with a wider range of usefulness than existing models.

*Apparatus.*—An additional iron strap is welded to the back of a standard open top infant oxygen tent frame, one inch above the bottom (Fig. 1). A plate of acrylic plastic (Plexiglass) measuring  $19 \times 17\frac{3}{4} \times \frac{1}{4}$  inches, is attached to the back of the frame by bolts. Two round openings, lined with  $\frac{1}{4}$  inch sponge rubber sleeves, are seen in the plate  $7\frac{1}{2}$  inches below the top and  $2\frac{1}{2}$  inches from the midline, which hold snugly in position a standard glass aerosol vaporizer and the metal oxygen-humidifier.<sup>1</sup> The whole is covered with a standard clear plastic canopy designed for the frame, in which two apertures were made to admit the long arm of the nebulizer and the nozzle of the oxygen-humidifier. Oxygen is delivered to these through a flow meter and a Y-shaped metal connecting piece with stop valves on each arm. In this way oxygen can be directed into either outlet independently. Water is provided for the humidifier from any reservoir placed at the same level or above the spray nozzle, such as a 1,000 c.c. glass intravenous bottle on a stand. The assembled equipment<sup>4</sup> is seen in Fig. 2.

*Operation.*—The infant is first clothed in a waterproof cap and jacket and placed in the tent through the sleevelike opening in the front of the canopy, with his head on a waterproof pillow. When using the oxygen-humidifier, the top of the canopy is left open over the rear third to aid in cooling the tent. Oxygen is run through the humidifier at 6 L. per minute and the droplet size of the spray is adjusted by the needle valve. By screwing in the needle valve a very fine mist can be introduced into the tent so that a humidity of 80 to 90 per cent can be achieved within one-half hour. The tent temperature then

From the Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine.

\*Obtained from Medicinal Oxygen Co., 3339 Butler St., Pittsburgh 1, Pa.

ranges from 70 to 79° F., the latter temperature being reached with a room temperature of 90° F. and oxygen content varies from 41 to 46 vols. per cent.<sup>3</sup> Water consumption by the unit amounts to 100 to 200 c.c. per hour and the attendant nurse must sponge out the accumulated water from time to time.

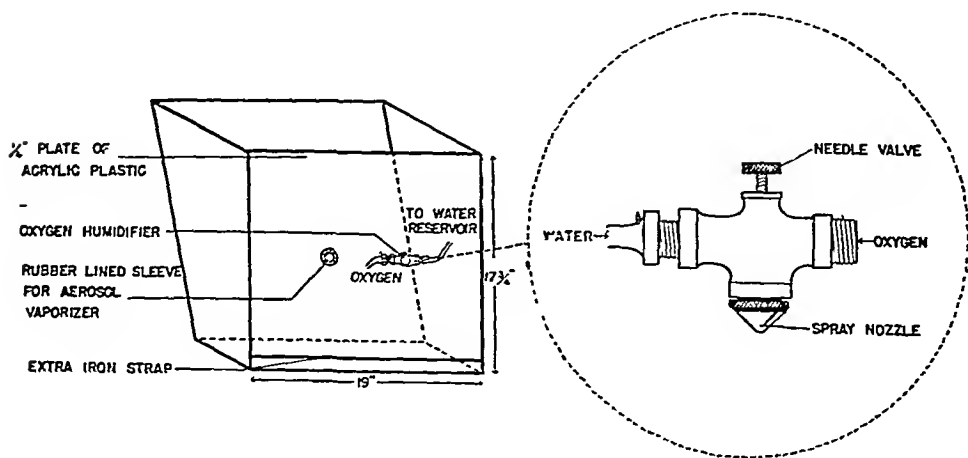


Fig. 1.

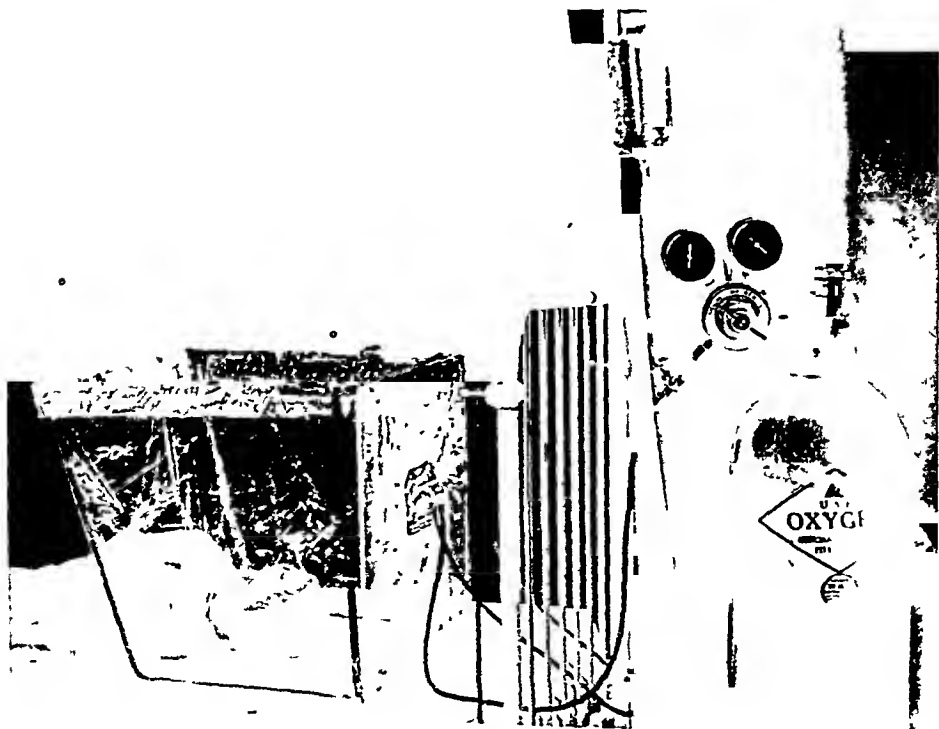


Fig. 2

Aerosol penicillin is administered every three hours in concentrations of 75,000 to 100,000 O.U. in 3 c.c. of normal saline, after redirecting the oxygen flow from the humidifier to the vaporizer. This antibiotic reaches the patient effectively as can be seen in Table I, where serum penicillin assays<sup>4</sup> were made after all the penicillin had been nebulized. During the administration of the aerosol, the top of the canopy is kept closed to reduce diffusion and the humidifier is cut off as the large droplets would probably precipitate the aerosol.

This equipment has been used principally for laryngotracheobronchitis cases but also is of use in conditions requiring aerosol antibiotics alone, such as cystic fibrosis of the pancreas. The children are contented in a tent where they can see all around, while the nurses can watch them with ease. The relatively high oxygen content is felt to be advantageous in dyspnea and the ease of administration of penicillin or streptomycin does away with the spasm associated with intramuscular injections.

TABLE I. LEVELS OF PENICILLIN IN SERUM AFTER AEROSOL PENICILLIN

PATIENT	AGE (MO.)	WEIGHT (LBS.-OZS.)	TIME* (MINUTES)	PENICILLIN (OXFORD UNITS)	
				DOSE IN 3 C.C. ISOTONIC SALINE	BLOOD LEVEL PER C.C. SERUM
C. M.	2	5 - 1	21	75,000	0.125
E. S.	3	7 - 12	21	75,000	0.062
J. W.	5	10 - 14	21	75,000	0.062
J. W.	5	10 - 9	18	100,000	0.250
J. W.	5½	10 - 13	20	75,000	0.125
M. Y.	8½	15 - 12	20	75,000	0.250
M. Y.	8½	15 - 2	30	75,000	0.250
W. J.	12	15 - 3	22	100,000	0.250
			195		0.000
M. F.	14	19 - 1	21	100,000	0.500
			170		0.000
A. McG	15	23 - 0	20	100,000	1.000

\*Time from start of penicillin.

#### SUMMARY

A new type of equipment is described which provides oxygen, humidity, and aerosol antibiotics for infants. It is possible to produce appreciable levels of serum penicillin and the relatively high oxygen content with a high humidity is felt to be valuable.

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# Case Reports

## TOXICITY OF CARONAMIDE

### REPORT OF A CASE

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THE use of Caronamide (4'-carboxyphenylmethanesulfonanilide) for the enhancement of penicillin blood levels has been advocated by several authors.<sup>1, 2, 3, 4</sup> They mentioned no toxic effects of Caronamide. Crossen<sup>3</sup> found no evidence of systemic toxicity in his series of cases, but stated that, as with any new compound, some type of sensitivity or toxic manifestation is likely to occur. Meads and associates<sup>5</sup> stated that mild toxic reactions were observed when Caronamide serum level exceeded 40 mg. per cent. Rapaport,<sup>6</sup> in a clinical evaluation of Caronamide in children, found no manifestations of toxicity that necessitated withdrawal of the drug. He reported rashes in three of the twelve patients, which apparently faded even while administration of the drug continued.

The following case of a patient with subacute bacterial endocarditis successfully treated with penicillin and Caronamide illustrates the toxic manifestations of fever, increased bleeding time, and increase in capillary fragility\* presumably caused by Caronamide.

### REPORT OF A CASE

E. R., an 11-year-old white girl, was admitted to Strong Memorial Hospital because of chills and fever existing for five days. For the previous two months the patient had: (1) a hacking cough and nasal discharge; (2) dyspnea on exertion; and (3) a weight loss of five pounds; although (4) she had experienced no joint or abdominal pains, nose bleeds, or urinary symptoms. Her past history revealed that she had cardiac enlargement and a murmur since the age of 10 months but without symptoms or disability. Her local physician reported no change in the long-standing heart murmur.

*Physical Examination.*—Temperature was 38.5° C.; pulse, 110; respirations, 20; blood pressure, 105/75. She was a well-developed and well-nourished girl 11 years of age, appearing moderately acutely ill. She was emotional and hypersensitive but quite cooperative. There was moderate injection of the nasal mucous membranes. Cardiac examination revealed enlargement to the left, a systolic thrill maximum at the pulmonic area, and a systolic murmur heard over the entire preecordium. No diastolic component was present. Pulsations were felt in dorsalis pedis arteries. There was no cyanoses or clubbing of fingers. No petechiae were found.

*Laboratory Findings.*—Red blood corpuscles were 5.4 million; hemoglobin, 13 Gm.; white blood corpuscles, 12,700. Differential polymorphonuclears, 83

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\*The capillary fragility was measured by means of an instrument consisting of a glass suction cup constructed to cover one centimeter of area and connected by rubber tubing to a mercury manometer. Negative pressure was obtained with a well-greased 50 c.c. syringe attached to the manometer. Negative pressure of 20 mm. of mercury for one minute on the extensor surface of the forearm of a normal child will show from 0 to 5 petechiae. In testing a child of comparable age and sex to the patient was used as a control. We have found this method superior to the standard tourniquet test because the same general skin area may be repeatedly used and the limited area of one centimeter makes counting the petechiae obtained relatively easy.

per cent; lymphocytes, 16 per cent; monocytes, 1 per cent; normal appearing red cells with adequate platelets. Urine normal. Throat culture: *Staphylococcus albus* and *Streptococcus viridans*. Blood culture: Positive for *Str. viridans* on first, third, fourth, and eighth hospital days; six subsequent blood cultures were sterile. X-ray and fluoroscopic findings revealed general cardiac enlargement with no specific diagnostic findings. Electrocardiogram indicated a right axis deviation and auricular enlargement.

A diagnosis of subacute bacterial endocarditis caused by *Str. viridans*, superimposed on a congenital heart lesion, was made on her sixth hospital day. It was felt that she did not have a patent ductus arteriosus. Specific therapy was given as follows: 50,000 units of penicillin every three hours for the first day, increased the following day to 200,000 units every three hours plus Caronamide 2.0 Gm. every four hours. Twenty-four hours after institution of therapy her fever had subsided. Penicillin blood level taken on the eighth hospital day was 2.56 units per cubic centimeter just before penicillin administration, and 5.12 units per cubic centimeter forty-five minutes after the drug was given. On her fourteenth hospital day, penicillin dosage was reduced to 200,000 units every six hours in view of the high blood level of penicillin. The patient had no temperature elevation above 38° C. from her seventh to her sixteenth day. She gradually improved both symptomatically and clinically.

On her seventeenth hospital day the patient's temperature rose to 38.2° C. and on the nineteenth and twentieth days reached 39° C. and 38.6° C., respectively. On the twentieth day petechiae were observed when a tourniquet was applied for the withdrawal of blood for culture. Studies revealed that (1) bleeding time and petechial count were increased; (2) prothrombin time, clotting time, and platelet count were normal; (3) blood cultures taken at this time were sterile. Caronamide was discontinued and penicillin dosage interval was shortened to every three hours. Within six days the petechial count dropped from nineteen to six.

On the twenty-sixth day, test doses of Caronamide were given—two doses, 2 Gm. each at a four-hour interval. At midnight the patient complained of nausea, vomiting, and inability to sleep. Her temperature rose to 39.5° C., and a scarletina-form rash of mild intensity was noted on her neck and chest. Twelve hours after the Caronamide, bleeding time and petechial count were increased. Urine examination revealed the presence of a reducing substance. This substance was identified as a mixture of fructose and a disaccharide. All symptoms subsided within twenty-four hours.

From the twenty-eighth until the forty-ninth day the patient's course was essentially uneventful. Blood cultures were sterile on the thirty-fourth and forty-first days. Penicillin therapy was stopped on the fortieth day, after thirty-five days of treatment and a total of forty-four million units.

In order to rule out a high penicillin level as an etiologic factor in the previously mentioned findings, nine days after the end of penicillin therapy two 2 Gm. doses of Caronamide were again given at a four-hour interval. Three hours after the second dose the patient complained of headache and general malaise, and in three hours more her temperature rose to 38.5° C. There was a marked increase in petechial count at this time, and a reducing substance identified as fructose and pentose was found in the urine. No significant alteration of bleeding time was noted during this episode. She was asymptomatic and afebrile twenty-four hours later.

Four days later the patient was started on 60 mg. Rutin every four hours in preparation for a repeat test with Caronamide, as before two 2 Gm. doses at a four-hour interval. There were no significant changes in the patient's condition either symptomatically or clinically with this test. The petechial count was elevated one day only, bleeding time and temperature were normal,

and no reducing substance was found in the urine. The patient was discharged clinically well fifty-eight days after admission.

## DISCUSSION

In Fig. 1 is illustrated the condensation of the therapeutic chart. The temperature curve represents the highest daily temperature recorded.

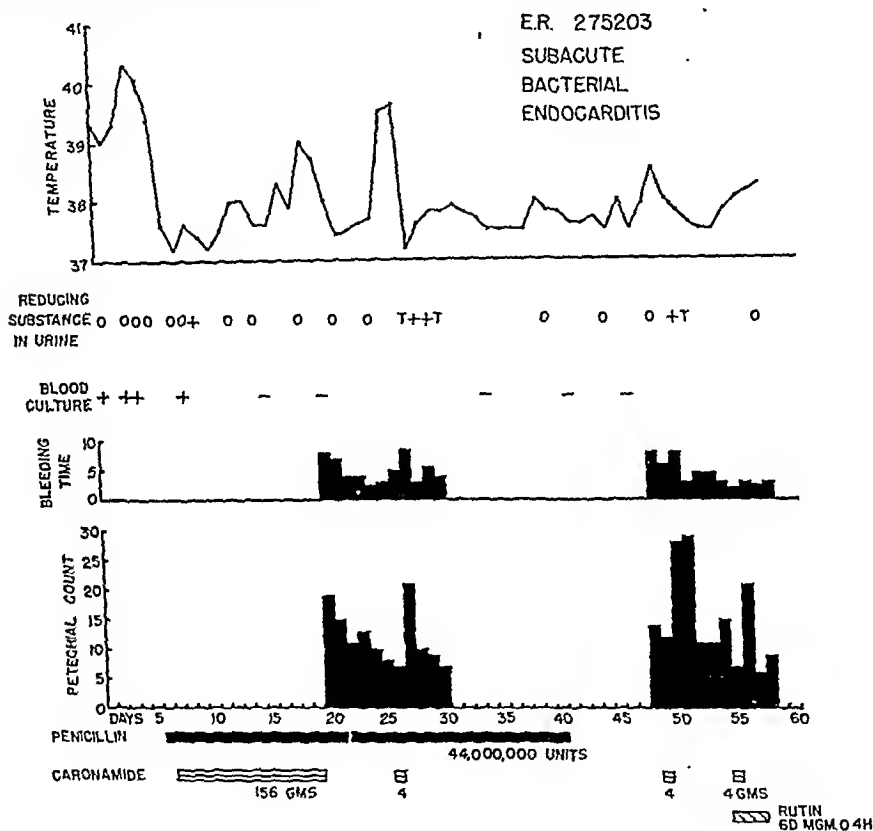


Fig. 1.

Although the symptoms and signs shown by this patient did not constitute serious toxic reactions, they did serve to confuse the picture of the patient's progress. The toxicology behind the Caronamide reaction as manifested by this patient is not clear. Rutin apparently had some beneficial effect in preventing capillary fragility and increase in bleeding time. Beyer and his associates<sup>7</sup> have studied extensively the pharmacology and toxicology of Caronamide, but did not experience reactions such as illustrated by our patient. It is felt that until more clinical and laboratory experience has been obtained, Caronamide should be used with caution.

## SUMMARY

1. A case of subacute bacterial endocarditis in an 11-year-old girl was successfully treated with penicillin and Caronamide.

2. A reproducible reaction consisting of fever, increased capillary fragility, and increased bleeding time occurred, presumably as a toxic effect of the Caronamide.



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## PULMONARY GANGRENE IN A CHILD FOLLOWING ASPIRATION OF TIMOTHY GRASS

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A VARIETY of vegetable foreign body that is commonly aspirated into the tracheobronchial tree is timothy grass (*Phleum pratense*). It is of interest because of the severity of the complications that may follow prolonged retention and because of the actions peculiar to this foreign body.

The most common complications of long-retained matter are lung abscess, suppuration, bronchiectasis, and, rarely, gangrene. The following case is presented because of the presence of the latter sequela.

### CASE REPORT

The patient, a white female infant aged 21 months, was admitted on Aug. 27, 1941, during an illness of twenty-three days' duration. At the onset she had swallowed some timothy hay and on the day following this began to cough up two to three ounces of foul-smelling sputum several times a day. Vomiting accompanied the cough, which became progressively worse. The latter persisted for four weeks, at which time the child began to whoop and assume the clinical picture of pertussis. A week prior to admission progressive dyspnea developed along with the symptom of pain and oppression beneath the sternum. There was severe anorexia and considerable weight loss.

Birth and development had been normal. The child had had exanthem subitum in April, 1941, followed by what the mother described as pneumonia for three days, although this could not be substantiated. There was no significant family history.

Examination on admission showed a well-developed but undernourished, somewhat emaciated, pale child weighing 19 pounds. Temperature was 101.4° F., pulse 120 per minute, respiration 50 per minute and labored. The skin and mucous membranes showed marked pallor. The breath had a foul odor. The tonsils were moderately enlarged and the pharynx showed an accumulation of mucopurulent material. Examination of the chest revealed markedly decreased breath sounds, marked dullness in the lower half of the right lung with many coarse, moist râles throughout this lung after coughing. The examination of the left lung showed hyperresonance with emphysematous sounds throughout. The heart was normal and not displaced. The spleen was enlarged 2 cm. below the left costal margin. The remainder of the abdomen was normal. There was clubbing of the fingers. The remainder of the physical examination was negative.

Initial hemogram showed 2.9 million erythrocytes with 6.5 Gm. of hemoglobin, 30,250 leucocytes with a predominance of polymorphonuclear cells. Urinalysis was normal. Roentgenogram revealed the heart and left lung to be normal. The right costophrenic angle was obliterated by a homogenous shadow extending to the level of the fifth interspace anteriorly, which had the appearance of fluid. Above this level and involving most of the lungs were homogenous shadows interspersed with spherical, translucent areas.

Institution of a high caloric diet, fluids, sulfathiazole, and postural drainage allowed for some recovery of purulent, yellow sputum but little clinical improvement. The temperature was elevated irregularly between 100 and 103°

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F. On August 30, bronchoscopic examination revealed the left main bronchus to be clear but slightly inflamed. The right was filled with foul, watery pus. The mucosa of the latter was inflamed and granulation tissue, which bled when touched, was visible. The filtered pus contained granulation tissue and numerous particles thought to be timothy hay. Posterior-anterior, right and left oblique x-ray examinations after bronchoscopy showed multiple abscesses and one large cavity 5.0 cm. in diameter.

On Sept. 3, a resection of a segment of the ninth rib under local anesthesia was performed with removal of several large pieces of necrotic lung tissue from the right pleural cavity. Microscopic examination of the tissue showed chronic inflammation but nothing characteristic of any specific infection. A large drainage tube was inserted into the pleural cavity. Subsequent x-ray showed no fluid level and showed that adequate drainage had been established. A slight right pneumothorax existed.

Postoperatively the child responded poorly. The temperature remained irregularly elevated between 100 and 102° F. The blood picture was improved slightly by transfusion of whole blood. Portable x-ray examination made two days before death showed the large cavity at the right lower lobe. Above the abscess cavity was a dense shadow. The right upper lobe was partially collapsed. Despite all measures the child expired on Sept. 10, 1941, thirty-seven days after the aspiration.

Autopsy findings were significant only in reference to the lungs. The left lung was normal except that pus could be expressed from the bronchioles throughout. The right lung showed only a shell of the lower and middle lobes. The entire lower cavity had been completely drained of necrotic tissue and pus. The upper lobe was made up of a small air-bearing area toward the hilus with the remainder consisting of three, intercommunicating, large cavities filled with dirty, foul-smelling, necrotic tissue and pus. The entire bronchial mucosa revealed a marked reddening and edema but was unobstructed and free of foreign body except at the distal end of the right lower bronchus where a piece of timothy hay 5 mm. in length was found. Considerable fibrosis was noted in the neighboring lung tissue. Microscopic examination of the lungs revealed a thickened pleura with an increase of connective tissue about the bronchi and blood vessels. Some epithelialization of the alveolar walls was evident, the latter being thickened. An infiltration of round and plasma cells and a few polymorphonuclears were seen. The fibrotic lung merged into necrotic tissue with only the connective tissue and a few round cells remaining. The appearance was that of a necrosis or gangrene of the lung.

#### DISCUSSION

Jackson and Jackson,<sup>1</sup> Clerf,<sup>2</sup> and Seydell<sup>3</sup> have reported cases of aspiration of timothy grass with records of removal by bronchoscopy and the discussion of bronchiectasis, abscess, and the more serious complications of metastatic supuration and severe hemorrhage. Butler and collaborators<sup>4</sup> were able to effect a cure in two cases of suppurative disease and bronchiectasis by lobectomy. Purcell<sup>5</sup> reported the case of a remarkable sojourn of timothy grass which was aspirated, then propelled by coughing throughout the bronchi to the periphery and eventually out through the chest wall. This case exemplifies the ability of timothy grass to be propelled along and anchored until coughing occurs, when it is moved along head first. Carter and Welch<sup>6</sup> also discussed the peculiarities of this foreign body and summarized eight cases, seven of which patients were benefited by lobectomy.

There are no characteristic bacteriologic patterns or pathologic changes attributed specifically to this foreign body. No previous mention has been made

of gangrene following aspiration and suppurative lung disease, although the sequence of events is not an unusual pattern. This may be due to some confusion between pulmonary abscess and gangrene. Abscess is a suppurative process due to pyogenic organisms, while gangrene is a more severe necrotizing lesion most often due to oral spirochetes, fusiform bacilli, and vibrios (Miller-Vincent organisms). The oral flora of young children does not contain these organisms. This probably explains the fact that there are fewer spirochetal abscesses in children than abscesses due to other organisms. As the oral flora changes from the pyogenic organisms and staphylococcus, the anaerobes are more prominent. Associated with this change are oral lesions, dental caries, and gingivitis.

Roma<sup>7</sup> in 1905 was the first to report the presence of spirochetes and fusiform bacilli in the lung, and he believed that carious teeth were the source. Pulmonary tissue may be invaded by Miller-Vincent's organisms to produce bronchitis, pneumonitis, gangrene, and pleurisy. Pulmonary gangrene is relatively uncommon in children and, like abscess, is most frequently found in the lower lobe. The nature of the cough reflex in young children and the failure to expectorate after coughing with swallowing of infective material, is an important factor in producing lung abscess and subsequent complications. The pathologic process of pulmonary gangrene is one of progressive and extensive molecular necrosis with the formation of cavities.

#### SUMMARY

1. A case of pulmonary gangrene following aspiration of timothy grass is presented.
2. A discussion of the foreign body and a brief review of the literature is included.
3. The pathologic and bacteriologic pattern is briefly discussed.

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## FATAL LEPTOSPIROSIS (WEIL'S DISEASE) IN A NEWBORN INFANT

CASE OF INTRAUTERINE FETAL INFECTION WITH REPORT OF AN AUTOPSY

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**L**EPTOSPIROSIS or Weil's disease is a specific infection usually caused by the *Leptospira icterohaemorrhagiae*.<sup>1</sup> This organism commonly infects wild rats, and human infections result from contact with the rat's excreta. Two other strains of *Leptospira*, *L. canicola* and *L. icterohemoglobinuriae vitulorum* produce a similar disease in dogs and cattle respectively, and both of these organisms have been known to produce Weil's disease in man.<sup>2, 3</sup> This disease is probably more common than generally suspected, since about 40 per cent of the human patients are not icteric, and since there is evidence of latent leptospiral infections in rats, dogs, and human beings.<sup>2</sup> It is believed that the leptospiras usually enter the body through the abraded skin, mucous membranes, or possibly the gastroenteric tract.<sup>1</sup> It has been shown, however, that *Leptospira* may infect fetal guinea pig tissues after passing through the placenta.<sup>4</sup>

This mode of infection may have occurred in one human patient whose case is recorded in the literature.<sup>5</sup> The purpose of this paper is to report the first proved case of fatal leptospirosis in a newborn infant. The course of the illness, the severity of the pathologic lesions, and the post-partum presence of agglutinins in a high titer in the mother's serum indicated that the infection of the infant was acquired during intrauterine life.

### CLINICAL HISTORY

H. S., a 29-year-old nulliparous female, was first seen in the third month of pregnancy. The only significant abnormalities noted on physical examination were severe dental caries, obesity, and thyroid hypertrophy. Her family and past history were noncontributory. Except for measles, chicken pox, and tonsillitis during childhood, she had never been ill. In the post-partum period the patient was questioned further on possible contacts with *Leptospira*. During the period from 1938 to 1943, she was a waitress in a restaurant infested with rats, but during this period was not ill at any time. She had two pet dogs from 1945 to 1948; these animals had not been ill. There was no other history of contact with animals or exposure to possibly contaminated water. Her husband was a mail carrier; he had had no illnesses and had no contact with animals.

The patient's prenatal course was uneventful except for slight dependent edema during the last two months of pregnancy. This responded to sodium restriction; there was no associated albuminuria on hypertension. Laboratory examination gave normal findings.

After a normal labor of three hours, the patient delivered a male infant weighing 3,450 Gm. on May 18, 1947. The delivery was facilitated by the use of forceps at the outlet and by an episiotomy.

The infant appeared normal at birth with good color and crying. While the skin was not icteric, the vernix caseosa and the amniotic fluid were stained with bile. He was breast fed until two feedings before death. The neonatal course was normal until thirty hours after birth, when moderate icterus appeared. At thirty-eight hours after birth, the infant became listless, icteric, cyanotic, dyspneic, and had several convulsions. The edge of the liver was palpable. The urine was dark, due to the presence of bile. Examination of the

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blood showed: hemoglobin 150 per cent (26.7 Gm. per 100 e.c.); red blood cells, 6.2 million per cubic millimeters; white blood cells, 11,600 per cubic millimeters; differential count, neutrophilic leucocytes 83 per cent, neutrophilic myelocytes 3 per cent, lymphocytes 14 per cent. There were 4 nucleated red blood cells per 100 white blood cells. Spinal puncture showed nothing abnormal. The infant's condition deteriorated rapidly, and death occurred six hours after the onset of the illness, and fourteen hours after the appearance of icterus.

#### AUTOPSY REPORT

The autopsy was performed ten hours after death. The body measured 52 cm. in length and weighed 4,175 Gm. The skin and scleras were mildly icteric. A small amount of sanguinous, mucoid fluid was present in the nose and mouth. There were no external hemorrhages. The attached umbilical cord was dry and contracted. The pleural and peritoneal cavities contained an increased amount of bile-containing fluid.

The thyroid and thymus glands showed nothing abnormal. The latter weighed 12 grams.

The heart weighed 20 grams, and had an entirely normal appearance except for a 2 mm. epicardial hemorrhage at the base of the pulmonic valve. There was a large amount of sanguinous, frothy fluid in the trachea and bronchi. Both lungs were heavy, and weighed 90 grams together. There were numerous subpleural hemorrhages, and the parenchyma was diffusely congested, edematous, and showed considerable intraalveolar hemorrhage.

The liver was enlarged and weighed 195 grams. There was rounding of the anterior edge. The hepatic parenchyma was firm and dark red in color, but its consistency was normal. There was no capsular wrinkling either before or after fixation. The gall bladder and extrahepatic ducts were explored, and were entirely normal. There was enlargement of the spleen, which weighed 23 grams. It had a firm, dark red, nonhyperplastic pulp. The pancreas was normal.

The adrenal glands were of normal size and weight. Their cut surfaces showed the usual neonatal congestion of the inner cortical layers. Each kidney weighed 15 grams, and neither showed gross pathologic changes.

The rest of the ~~autopsy~~ was normal except for the testes, which showed diffuse . . .

The great vessels, bone marrow, gastroenteric tract, and mesenteric lymph nodes showed nothing abnormal.

The scalp, skull, and intracranial contents were entirely normal grossly. The brain was not icteric.

#### MICROSCOPIC DESCRIPTION

The heart was normal except for a few small perivascular hemorrhages in the myocardium. There was marked vascular congestion in the lungs, and in addition there was recent extensive hemorrhage in the interstitial tissues and within the alveolar and bronchial spaces. Many alveoli were filled with serous fluid, but there was no inflammatory reaction.

There was extensive destruction of the liver with disruption of the cords of hepatic cells (Fig. 1). There was tremendous dilatation of the sinusoids, which were distended with blood. The portal triads and central veins were still visible. Large numbers of hepatic cells had been destroyed and had disappeared. Most all of those remaining showed degenerative and necrotic changes, including cytoplasmic vacuolization and swelling, and swelling or pyknosis of the nuclei. Many remaining cells were detached from their basement membranes. While all the hepatic cells were involved in the degenerative process, those adjacent to the portal triads were better preserved. Both the triads and sinusoids contained moderately abundant hemopoietic tissue. There was no evidence of stasis of bile either in the small bile ducts or biliary canaliculi. Nowhere was there evidence of regeneration of the hepatic cells.

The splenic lymphoid follicles were normal; the splenic pulp was congested, and contained large numbers of well-differentiated hemopoietic elements. The gall bladder and pancreas showed nothing abnormal. Submucosal hemorrhages were present in sections from several levels of the gastroenteric tract.

There was a normal degree of neonatal capillary congestion and cellular degeneration of the inner cortical layer of the adrenal glands. There was no structural alteration of the renal glomeruli, but glomerular spaces often con-

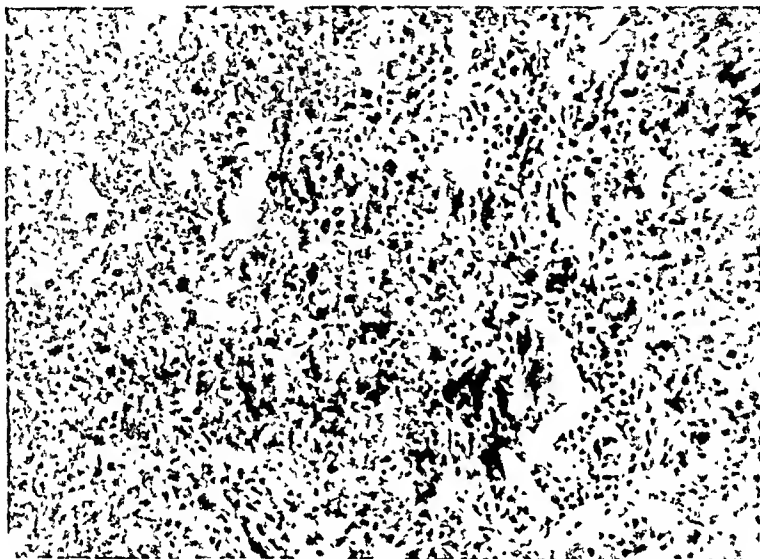


Fig. 1.—Liver showing parenchymal necrosis and sinusoidal engorgement. Hematoxylin and eosin stain ( $\times 210$ ).

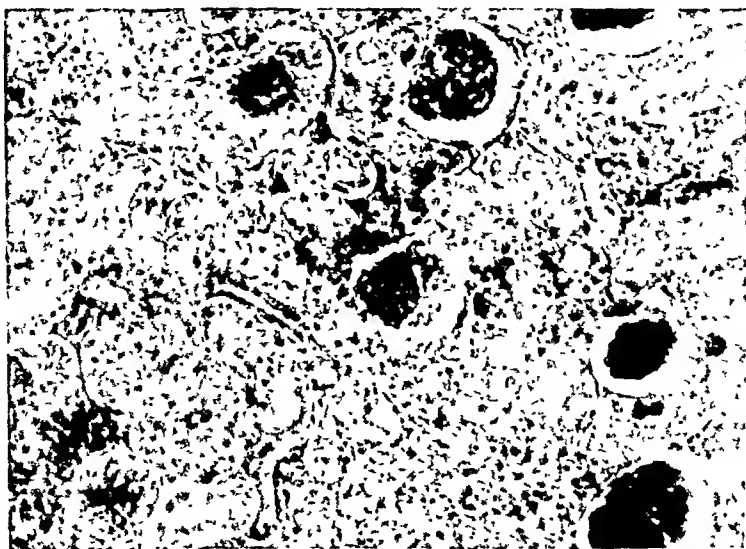


Fig. 2.—Kidney showing tubular degeneration. Hematoxylin and eosin stain ( $\times 210$ ).

tained precipitated protein and desquamated epithelial cells. There were striking degenerative changes in the tubular epithelial cells, particularly of the proximal and distal convoluted groups (Fig. 2). Similar but less marked alterations of the tubules comprising Henle's loops were noted, but the collecting tubules were lined by normal epithelial cells. The damaged tubular cells were markedly swollen, vacuolated, and had abundant eosinophilic cytoplasm. In addition, many had swollen, pale, or pyknotic nuclei. The nuclei were completely absent in some necrotic cells which were desquamating into the tubular lumens. Some tubules contained protein and epithelial cellular casts, and a few were occluded by casts containing bile. There was marked vascular congestion of the entire renal tissue with small perivascular hemorrhages in some areas. While small hemopoietic foci were encountered, there was no renal inflammatory reaction. The renal pelvic tissues, bladder, and prostate gland showed nothing abnormal.

The testicular blood vessels were congested, and there were many perivascular hemorrhages. The aorta was normal.

While there was considerable hemopoietic activity in the mesenteric and pre-aortic lymph nodes, there were no hemorrhages or inflammatory reaction. The thymus gland was normal except for several interstitial hemorrhages. The thyroid gland and pituitary gland had a normal structure. The sternal marrow presented normal appearing hemopoietic tissue with normal proportions of cells of the erythroid, myeloid, and megakaryocytic series.

In the brain there was moderate vascular congestion with a few small perivascular hemorrhages. There was slight hemorrhage in the subarachnoid space about the base of the brain, and this was accompanied by a mild lymphocytic infiltration.

A section through the umbilicus showed only thrombosis of the large vessels, and minimal acute inflammatory infiltration of the segment of necrotic umbilical cord.

Sections of the liver and kidneys were stained by the Dieterle and Levaditi silver impregnation methods. Rare leptospiras were found in the liver. Several typical organisms were demonstrated in the renal tubular lumens. Some of these had an "S" or "C" shape. These organisms could not be photographed satisfactorily. In the tubular cells and lumens were many silver-impregnated structures which were consistent with fragmented leptospiras.

The mother's blood type was 4 O Rh<sub>1</sub>Rh<sub>2</sub> (Hr' neg.), the father's type was 2 A Rh<sub>1</sub>rh (Hr' pos.), and the infant's type was 4 O Rh<sub>1</sub>Rh<sub>2</sub> (Hr' neg.). There was no agglutination of the infant's red blood cells (obtained at autopsy) by the mother's serum when the cells were suspended in saline, bovine albumin, or AB plasma.

Since the microscopic appearance of the hepatic and renal tissues was consistent with the lesions of human leptospirosis, and also because the appearance was almost identical with the lesions of several cases of canine leptospirosis being examined in the laboratory during the same period, agglutination tests with the mother's serum and two strains of *Leptospira* were done at the Hooper Foundation, University of California Medical School, by Dr. B. Eddie. The results were reported by her as follows:

DATE	STRAIN	TITER		
June 2, 1947	<i>L. icterohemorrhagiae</i>	1:10,000	1+	
	<i>L. canicola</i>	1:1,000	4+	1:10,000 1+
June 14, 1947	<i>L. canicola</i>	1:2,560	4+	
Sept. 9, 1947	<i>L. icterohemorrhagiae</i>	Negative		
	<i>L. canicola</i>	Negative		
Dec. 29, 1947	<i>L. icterohemorrhagiae</i>	Negative		
	<i>L. canicola</i>	Negative		



The mother's postpartum course was entirely uneventful. In 1947 to 1948, the patient had a second normal pregnancy, and on July 26, 1948 delivered a normal male infant who remains alive and well. There was no agglutination of either *L. icterohaemorrhagiae* or *L. canicola* by the mother's serum or by serum from the infant's cord taken at the time of birth. (Dr. B. Eddie).

#### COMMENT

Costa and Troisier,<sup>6</sup> and later Takagi,<sup>7</sup> showed that *Leptospira* could penetrate the placenta of guinea pigs. Hiyeda<sup>5</sup> reported a case of abortion of a 4-month-old fetus by a woman who had been ill with Weil's disease for twenty days. While both the fetus and its cord were icteric, histopathologic examination of the fetal tissues showed no lesions, and no leptospiras were demonstrable. That author believed, however, that the fetus was infected. Saenz<sup>8</sup> and Das Guptas<sup>4</sup> both were able to demonstrate in guinea pigs the transmission of *Leptospira* from the mothers to their fetuses; organisms were found in the fetal tissues.

In the case herein reported, the histopathologic lesions in the infant's tissues were typical of those of leptospirosis as may be seen in the human, canine, and bovine forms of the disease.<sup>1, 3</sup> The severe hepatic necrosis, the renal tubular degenerative lesions, and the multiple hemorrhages in many tissues are characteristic of the process. *Leptospiras* were demonstrated in the infant's liver and kidneys.

That the infant was infected before birth is indicated by the following: (a) the hepatic lesion was too extensive and severe to have developed in the forty-four-hour period following birth, (b) the vernix caseosa and amniotic fluid were stained with bile, and (c) the presence in the mother's serum of agglutinating antibodies in high titers to both *L. icterohaemorrhagiae* and *L. canicola* two weeks after delivery, with their subsequent decrease and final disappearance during the next few weeks. It seems most probable that the mother had latent leptospirosis during late pregnancy. The complete lack of clinical manifestations in her suggests that the fetal tissues were more susceptible to invasion than were the maternal ones. Had the correct pathologic diagnosis in the infant been made promptly, a search for *Leptospira* in the mother's blood and urine might have been done. The source of infection in this case remains unknown.

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## Clinical Conference

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CONFERENCE AT THE MT. SINAI HOSPITAL, NEW YORK, N. Y.

DR. JEROME L. KOHN    JUNE 24, 1948

DR. SAMUEL KARELITZ    AUG. 26, 1948

### Case 1. Diaphragmatic Paralysis Associated With Erb's Palsy

DR. ROBERT D. LONDON (Resident in Pediatrics).—On March 17, 1948, a 6-week-old white male infant was admitted to The Mount Sinai Hospital because of intermittent cyanosis, rapid respirations, difficult feeding, and vomiting of six weeks' duration. He was born at term of a primiparous mother. The pregnancy was uncomplicated. The labor lasted twenty-one hours and the child was extracted from the breech position by forceps application to the aftercoming head. His birth weight was 3.1 kg. The child required artificial respiration for ten minutes. A flaccid paralysis of the right arm with slight movement of the fingers and wrist was noted at birth. He remained in the hospital for five days, during which time tachypnea and fatigability on feeding necessitated the use of a Breck feeder. A roentgenogram of the chest on the third day revealed a slightly elevated diaphragm on the right side but no other abnormalities.

At home he fed poorly, was tachypneic, and vomited frequently in a non-projectile manner both during and shortly after feedings. At 3 weeks of age he was admitted to a hospital because of vomiting and tachypnea. After ten days he was discharged home without a diagnosis and without alteration of symptomatology. In the next ten days respiratory difficulty became severe and cyanosis became constant. He presented no other respiratory symptoms except for mild cough associated with fever which lasted one day. His weight remained stationary since birth.

On admission to the hospital he appeared critically ill and was deeply cyanotic. He was poorly nourished and his skin was pallid. Respiratory distress was prominent with substernal retractions and a rate of 80 per minute. Respiratory excursions on the right were less than those on the left. There were no abnormalities of the head, eyes, ears, nose, or throat. Paradoxical diaphragmatic movement of the right side with deep subcostal retraction during inspiration was noted. Hyperresonance was elicited anteriorly above the fourth intercostal space and posteriorly above the level of the midscapula. Below these regions dullness was obtained. A few fine inspiratory crackles were heard below the right scapula and over the anterior lung field to the anterior axillary line; posteriorly resonance was somewhat diminished. Breath sounds were diminished throughout, with fine inspiratory crackles over the left lower lobe posteriorly. The heart sounds were of maximal intensity in the left anterior axillary line. No abnormal heart sounds were heard. The right arm moved poorly, slight flexion was noted at the elbow, and a fist could be made.

Fluoroscopy of the chest revealed the heart and mediastinum to be displaced to the left. Paradoxical motion and elevation of the right diaphragm associated with shift of the mediastinum to the left on inspiration was evident. The right lung appeared hyperaerated and the left lung was diffusely hazy.

A chest film revealed an extreme degree of elevation of the right diaphragm which extended upward to the level of the fourth intercostal space posteriorly. The liver was displaced upward and medially; distended coils of bowel extended upward along the lateral portion of the right diaphragm. The heart and mediastinal structures were displaced into the left chest.

It was felt at that time that the child had an injury involving the roots of the phrenic nerve and upper portion of the brachial plexus which probably was secondary to the trauma of birth.

He was kept in an oxygen tent continuously from the time of admission, but despite this he remained tachypneic until he expired forty-four days later. The respiratory rate varied, but was most commonly from 60 to 80 per minute. Because of this accelerated rate, feeding was a persistently difficult problem. This was further aggravated by displacement of the stomach and a tendency to swallow and accumulate air which made vomiting a frequent hazard. Gavage feedings were employed and a thickened formula was used. Despite an adequate caloric intake and the retention of feedings throughout most of his course, he gained only 0.25 kg. Repeated examinations of the chest failed to show any significant alteration of the findings noted on admission. The right lung remained partially aerated and the shifted mediastinum encroached on the left chest, which prohibited proper aeration of the left lung. Attempts were made to improve this situation by varying the position of the child, but were to no avail.

The Erb's palsy at no time showed evidence of improvement. The hand was weakly clenched occasionally in a fistlike manner and there were weak flexion movements of the wrist and elbow.

During the course of the illness he was given penicillin prophylactically with success, although repeated white blood cell counts showed intermittent leucocytosis with a differential shift to the left. He remained afebrile throughout his course.

Beginning about twelve days before his death occasional rapidly developing periods of deep cyanosis associated with the regurgitation of small amounts of formula into the oropharynx occurred. The episodes were readily terminated by aspiration of the material.

On the forty-fourth hospital day he suddenly went into collapse. On this occasion aspiration of the mouth and oropharynx produced no exudate or vomitus. Examination of the chest revealed dullness to percussion everywhere with absent breath sounds over the entire right lung field. A total atelectasis of the right lung and a diffuse pneumonia of the left lung were suspected. He became progressively apathetic and expired.

Post-mortem examination by Dr. L. Turner and Dr. M. Baxt, including a dissection of the brachial plexus on the right side and the spinal cord, revealed the following findings.

The anterior roots of C5 and C6 on the right were found avulsed at their junction with the cord. The branches of the brachial plexus and both phrenic nerves were dissected in their entirety and appeared grossly intact. The major portion of the right phrenic nerve arose from C5, receiving a small twig from C4. The right leaf of the diaphragm was elevated to the level of the second rib and it was stretched, thinned, translucent, and contained a sparse amount of muscle fibers. The right lung was almost entirely atelectatic and the left lung contained focal areas of atelectasis. There was no evidence of pneumonia. The heart weighed 34 grams (normal 23 grams) and there was evident a generalized myocardial hypertrophy.



Fig. 1.

Weil-Weigert myelin sheath stains disclosed a complete absence of myelin in the right phrenic nerve and an almost complete absence with a few intact fibers in the right musculocutaneous nerve.

The right leaf of the diaphragm contained markedly atrophic musculature with hyaline degeneration and loss of striation of the muscle fibers. The right lung was markedly atelectatic and the left lung contained focal areas of atelectasis.

#### DISCUSSION

This case is essentially similar to other instances of diaphragmatic paralysis associated with Erb's palsy. The history of a difficult delivery, Erb's

palsy noted at birth, and respiratory difficulty developing at or shortly after birth are frequently described features. These, plus the fluoroscopic findings of an elevated diaphragm and paradoxical respirations, make the diagnosis of phrenic nerve injury almost certain. The most common diagnostic errors are congenital heart disease, pneumonia, intracranial hemorrhage, atelectasis, congenital malformations of the respiratory tract, and diaphragmatic hernia.

With adequate medical care which is primarily prevention of infection and aspiration and the administration of oxygen as indicated, about 80 per cent of the infants recover.

Usually the injury consists of stretching or pressure on the phrenic nerve root. Avulsion of nerve roots as was found in this case here described has not been noted. It is, therefore, unknown whether infants recover after such extensive damage.

DR. KOHN.—Is there any useful surgical procedure to alleviate or correct the altered physiology this condition produces?

DR. LONDON.—A discussion with thoracic and pediatric surgeons about this problem failed to reveal any known surgical technique to handle the problem.

DR. MOLOSHOK.—Is the diaphragmatic paralysis always associated with an Erb's palsy?

DR. LONDON.—A review of thirty-two described cases disclosed that twenty-two were associated with Erb's palsy and ten were not.

DR. KARELITZ.—Do you often find complete avulsion of nerve roots associated with this injury?

DR. LONDON.—A search of the literature failed to uncover a similar case.

DR. KOHN.—Is this injury always associated with breech deliveries?

DR. LONDON.—To the best of my knowledge, yes.

#### SUMMARY

DR. KARELITZ.—In summary, this is a case of Erb's palsy and diaphragmatic paralysis due to trauma of the brachial plexus with avulsion of the phrenic nerve from its roots. It was incurred in the extraction of the child in breech position. While the child manifested respiratory difficulty early, it became severe after infections set in. All therapy was without avail.

We have been unable to find record of other cases of phrenic nerve palsy in the newborn infant in which complete avulsion of the nerve roots was demonstrated.

#### Case 2. Bleeding Peptic Ulcer

DR. BENNETT L. GEMSON (Assistant Resident in Pediatrics).—This was the first Mount Sinai Hospital admission of a 5½-year-old white boy who was well until ten days prior to admission, when he developed a mild, nonbloody diarrhea associated with vomiting and a temperature of 101.8° F. A younger brother had diarrhea just prior to this illness, the patient's mother developed

diarrhea coincidentally with the patient, and the father developed this same symptom one week later.

The patient's diarrhea and fever subsided in one day after he was given Peptobismol and a "chalk" medicine. During this episode, however, and in the following five days, the patient had recurrent bouts of moderately severe, midline, abdominal pain; the pain would subside spontaneously, and was frequently associated with nausea, but never with vomiting. The patient was constipated after the diarrhea, and so, seven days prior to admission, was given two tap water enemas with return of a few small, hard, fecal masses. The following day, six days prior to admission, he was given milk of magnesia and two days later, four days prior to admission, castor oil, with a temperature elevation that evening to 101° F. Early the next morning, three days prior to admission, the patient had a large, nonbloody, liquid bowel movement followed by weakness and subsequent passage of three loose movements containing bright red blood in moderate amount. The fever then subsided, as did the abdominal pain. For two days prior to admission there still were frequent, tan-colored stools which did not contain gross blood; however, when the patient's perianal region was wiped there was bright red blood on the paper. Concomitantly the patient showed progressive asthenia and pallor, and on the day prior to admission he developed some pain in the neck, ringing in the ears, and swelling around the eyes, with a temperature rise to 104° F.

There was no previous history of anemia, hematemesis, melena, trauma, ingestion of foreign material, or bleeding tendency in the patient or his family.

Family history was noncontributory, and review of systems was negative.

Physical examination revealed a well-developed, well-nourished white boy, somewhat disoriented, with marked pallor, cold, clammy skin, and rapid, thready pulse, presenting a picture of circulatory collapse. The pulse rate was 180 per minute, and the blood pressure 106/0. Because of the patient's critical condition further examination was necessarily brief. The lungs were clear to percussion and auscultation. The heart showed marked tachycardia. Sounds were of fair quality, and there were no murmurs. On careful abdominal palpation no liver, spleen, or other masses were palpated.

Significant laboratory findings were: hemoglobin, 2.75 Gm.; white blood cells, 27,000; segmented polymorphonuclear leucocytes, 60; nonsegmented polymorphonuclear leucocytes, 12; lymphocytes, 28. The blood smear showed two normoblasts per 100 white blood cells, moderate aniso- and poikilocytosis, but no abnormal cells. The urine was negative. The blood group was A, Rh positive. The bleeding time was 4 minutes and the clotting time 3.5 minutes.

The patient was given nothing by mouth, and sedated with codeine and phenobarbital by injection. He was placed in an oxygen tent, and a blood transfusion was started.

After receiving 100 c.c. of blood, the patient appeared somewhat improved, with a rise in blood pressure to 130/80 and a fall in pulse to 144. Six hours after admission the hemoglobin had risen to 9.5 Gm. At this time profuse rectal bleeding with a large number of clots was noted. Another 500 c.c. of blood was given, together with 5 c.c. of calcium gluconate.

During the second hospital day there were four episodes of massive rectal bleeding. The hemoglobin fell from 9 to 6 Gm. with 2,260,000 red blood cells, and a fourth transfusion of 500 c.c. was given. The blood pressure ranged between 110/50 and 130/80, and the pulse between 136 and 150. The patient was restless and crying most of the day.

On the third hospital day, the patient continued to pass large, liquid, bloody stools, and the hemoglobin had fallen to 5 Gm., with 48,000 white blood cells. A fifth transfusion of 500 c.c. was started. Because bleeding was uncontrolled after three days of conservative treatment, he was seen by a surgeon, who felt the most likely causes of his bleeding were (1) a polyp of the large bowel, (2) a bleeding Meckel's diverticulum, or (3) a reduplication of the intestine with bleeding from the reduplicated loop. Bleeding peptic ulcer was thought to be unlikely in view of lack of vomiting or hematemesis. Exploration was advised.

The patient was given an additional 500 c.c. of blood, and taken to the operating room shortly after noon.

The abdomen was explored through a right midrectus incision. There was a small amount of clear amber fluid in the peritoneal cavity. The intestinal tract from the lower sigmoid up to the upper third of the ileum was filled with darkly colored blood. It was difficult to ascertain with certainty whether there were any polyps in the colon or sigmoid due to the blood in the bowel. There was no evidence of a Meckel's diverticulum or of an intestinal reduplication. The stomach was visualized. It did not contain blood and felt normal. The head of the pancreas felt slightly enlarged and hard, as is average in a child of this age. The duodenum was palpated but not visualized, and although the pylorus felt slightly indurated there was nothing to suggest by palpation that an ulcer was present.

Postoperatively, bloody drainage was obtained from the Levin tube and the patient continued to have bloody stools. After an additional 500 c.c. of blood, his hemoglobin was only 6 Gm.

On the fourth day (the first postoperative day), bloody drainage per Levin tube and per rectum continued, and the patient appeared worse. The blood pressure fell to 98/0 with a pulse rate of 164. After receiving 1,200 c.c. of blood, the hemoglobin was 5 Gm. Two more 500 c.c. blood transfusions raised the hemoglobin to 9 Gm. and the blood pressure to 140/70. He was offered small amounts of skimmed milk by mouth. In the late afternoon he passed a polypoid mass by rectum, measuring about  $1\frac{1}{2}$  by  $1\frac{1}{2}$  cm., lobulated and yellow stained. Pathology report after examination of a frozen section was necrotic tissue, possibly a polyp, but it was not possible to state its origin with certainty. This finding, although not definite, made us feel that we were dealing with a case of multiple polyps; otherwise, a second exploration might have been attempted.

On the fifth day (the second postoperative day), bleeding per rectum continued, and the patient was extremely restless. He received 1,500 c.c. of blood, yet his hemoglobin never rose above 6 Gm. The blood pressure ranged

between 100/40 and 132/70. Toward evening he had his first episode of hematemesis, vomiting about 60 c.c. of bloody fluid.

During the sixth day (the third postoperative day), his condition deteriorated. There were frequent hematemeses and bloody stools. He was sedated heavily, given Hykinone, ascorbic acid, and calcium by mouth, and received two additional transfusions. His hemoglobin ranged between 5.5 and 6.0 Gm., blood pressure between 120/40 and 100/0, and pulse between 180 and 200. Toward evening he appeared confused. Surgery was not considered indicated.

On the seventh day (the fourth postoperative day), bleeding per rectum persisted. Early in the morning the patient's pulse was rapid and thready, and the respirations were increased. He began to vomit large amounts of bright red blood and passed continual dark red liquid per rectum. At 5:45 A.M. respirations ceased. He had received a total of 7,820 c.c. of blood and a host of medicaments in an unsuccessful effort to control his gastrointestinal bleeding, whose source remained a mystery up to the time of death.

DR. KARELITZ.—What were the findings at post-mortem?

DR. GEMSON.—At post-mortem, examination of the unopened stomach and duodenum failed to reveal any abnormality, but with these organs open an acute peptic ulcer of the duodenum was found, with erosion of the superior pancreaticoduodenal artery. There was a large amount of blood in the gastrointestinal tract. The tissues were moderately icteric. There was 400 c.c. of fluid in the peritoneal cavity and 300 c.c. in each pleural cavity. There was a focal fibrinous pleuritis of the right lower lobe, partial atelectasis of all lobes of the lung, and petechial hemorrhages of the lungs and pericardium.

Of particular interest in this case were: (1) the difficulty in making a proper diagnosis, (2) the failure of conservative treatment in controlling the bleeding, and (3) the inability to locate the source of the bleeding at exploratory laparotomy and (4) the inability to diagnose the presence of the ulcer at post-mortem examination of the unopened stomach.

Dr. Nathan Schifrin, Assistant Resident on Pediatrics, who admitted this patient, ventured an admission diagnosis of "possible peptic ulcer with hemorrhage." Other members of the Pediatric Staff were less specific and offered the possibilities of a bleeding ulcer of Meckel's diverticulum, a bleeding polyp, and a bleeding gastric or duodenal ulcer as the most likely diagnoses. The surgeons felt that the absence of hematemesis until the terminal stages of hemorrhage made peptic ulcer of the stomach or duodenum improbable.

DR. LONDON (Resident on Pediatrics).—The appearance of bloody drainage via the Levin tube postoperatively might have led one to suspect that the source of the bleeding was high up in the gastrointestinal tract, stomach, or duodenum.

DR. KARELITZ.—I believe that Dr. London is correct, but the passing of the polyp-like mass confused the issue. Would you say a few words about the occurrence of peptic ulcer in childhood?



DR. GEMSON.—Peptic ulcers of the stomach and duodenum, although rare, may occur at any age and have been described in stillborn and even premature infants. They are more numerous in infancy than in childhood, and tend to run a more acute course than they do in adult life.

Ulcers are asymptomatic in a high percentage of cases, and are frequently unsuspected until autopsy examination. A silent clinical course is the rule in infancy, but after the first year or two symptoms are similar to those of adults.

Ulcers in the young may give rise to (1) malnutrition and repeated gastric upsets, (2) exsanguinating and even fatal hemorrhage, (3) perforation, and (4) mechanical obstruction from scar tissue near the pylorus.

Treatment is much the same as in adults. Medical treatment usually effects a cure in uncomplicated cases. Hemorrhage is usually tolerated poorly, and blood should be administered sooner and more liberally than is the custom with adults.

Surgical treatment consists of gastroenterostomy for mechanical obstruction, simple closure for perforation, and ligation of the bleeding vessel (if it can be located) for hemorrhage.

DR. ANFANGER.—What are the conditions most likely to cause massive gastrointestinal hemorrhage via the rectum?

DR. GEMSON.—A bleeding Meckel's diverticulum, a polyp anywhere in the colon, and a peptic ulcer are the most probable causes of profuse hemorrhage from the gastrointestinal tract, aside from hematologic disorders which could be readily diagnosed by appropriate blood studies. Esophageal varices, as well as peptic ulcer, almost invariably produce hematemesis.

DR. E. GOODMAN.—I have reviewed the records at Babies' Hospital and found reference to three cases of duodenal ulcer in children, all occurring at 11 to 12 years but with histories dating back to 8 years of age.

I am surprised that the children who bled did not vomit blood.

DR. KARELITZ.—In the past two years I have had the rare opportunity to see four cases of duodenal ulcer in childhood. The first patient, a boy of 13, fainted while standing in the food line at school and did the same the next day. His hemoglobin was 6 Gm. and the stools were tarry. He did well on bed rest, two transfusions, a residue free diet, and alkali. He has had no recurrence of symptoms to date. This boy had epigastric discomfort a year before his bleeding episode, and was told by a doctor to take bicarbonate of soda. Finding relief, he did not complain again but took bicarbonate of soda when pain recurred. He also learned that eating relieved him of his pain.

The second was a boy of 14 years who, while returning from a ranch in Wyoming, vomited all his meals on the train and continued to vomit everything ingested for the next seven days. He had slight tenderness in the epigastrium on physical examination. Radiologic examination revealed some pyloric stenosis and a duodenal ulcer. Gastric contents contained blood. He, too, has done well on a dietary regime.

The third was a 16-year-old girl who fainted while studying. She was found to be pale, her hemoglobin was 6.5 Gm., and the stools were tarry.

There had been no history of abdominal pain nor of dyspepsia. She had dieted severely for some time and had lost 35 pounds. She did well on a low residue diet with alkali.

The fourth was the patient described here by Dr. Gemson.

Thus only one of the four vomited. Of the three who bled, none vomited. The histories of all four children reveal domestic disturbances which resulted in behavior defects.

In the previous twenty years of my pediatric practice I never have had a case of duodenal ulcer. Gastroenterologists are prone to think that duodenal ulcer has its incipency in childhood. Can it be that the world turmoil is affecting our youth to the extent of helping to produce more psychosomatic diseases such as duodenal ulcers?

### Case 3. Acute Idiopathic Hemolytic Anemia With Hemoglobinuria

DR. NATHAN SCHIFRIN (Assistant Resident in Pediatrics).—This is the first Mount Sinai Hospital admission of a 23-month-old male child brought here because of dark urine of three days' duration. The child was apparently well until three days ago when he had one episode of vomiting. Following this the child had a shaking chill and a temperature elevation to 101° F. One-half an Empirin compound tablet was given. Because of constipation for over forty-four hours he was given a soapsuds enema. Late that afternoon dark urine was passed. The pediatrician was summoned and on physical examination acute follicular tonsillitis was noted. Penicillin 25,000 units every three hours was started intramuscularly. The finding of acute tonsillitis and the history of dark urine made the physician suspect acute nephritis. The white blood count was 8,900 per cubic millimeter, the hemoglobin was 8.5 Gm. per 100 c.c. The temperature returned to normal about twelve hours after the starting of the penicillin therapy, but the urine continued to be dark. A urine specimen obtained the next day contained laked red blood cells and granular casts. Several other urine specimens were examined with the same findings. It was felt that there were not enough red blood cells to account for the dark color. Spectroscopic examination of the urine by Dr. Daniel Stats showed hemoglobin and methemoglobin to be present. On the day before admission the white blood count was 5,050, and hemoglobin was 7.0 Gm. The smear showed rare spherocytes and the reticulocyte count was 5 per cent. Slight icterus of the sclerae was noted on this day. The patient was passing urine frequently, but only 15 to 30 c.c. at a time. He was anorectic, his pallor was increasing, and he continued to pass dark urine. He was, therefore, hospitalized. There was no family history of allergy, no new foods had been included in the diet, no unusual medication had been tried before the onset of this episode, and the patient had had Empirin compound tablets before without any ill effect. There was no history of having ingested any fava beans. The mother's blood Wassermann was negative at the time of this child's birth.

On admission the patient, a well-developed, and well-nourished child, was acutely ill but in no distress. He appeared very pale and presented a lemon

yellow appearance. The sclerae were slightly icteric. The tonsils were enlarged and a white exudate was present on the left. The cervical lymph nodes were shotty in the anterior and posterior cervical chains bilaterally. The lungs were clear to percussion and auscultation. A short systolic murmur was heard at the apex. The liver was palpable one centimeter below the costal margin. The spleen was not palpable. He was afebrile.

On admission the red blood count was 2.5 million with 7.0 Gm. of hemoglobin. White blood count was 10,500 and the platelets were 150,000. The patient's blood type was group A, Rh positive, Rh' positive and Rh'' negative. Hypotonic saline fragility test of the patient's red blood cells revealed hemolysis starting at 0.44 per cent saline and complete at 0.16 per cent saline. Heat resistance test for paroxysmal nocturnal hemoglobinuria was negative. Examination of the patient's serum for agglutinins revealed no agglutination in albumin or saline at 37° C. against homologous red blood cells. At 4° C. there was a titer of agglutinin of 1:10 against homologous red blood cells. Against heterologous compatible red blood cells at 37° C. there was no agglutination in albumin or saline; at 4° C. the titer of agglutinins was 1:20. Thus, no significant rise in agglutinin titer was demonstrable. There were no hemolysins against compatible red blood cells. The Donath-Landsteiner test was negative. The course of illness, the normal red blood cell fragility, the negative heat resistance test, the hemoglobinemia, and hemoglobinuria made the diagnosis of acute hemolytic anemia of unknown etiology most probable.

The patient was promptly transfused with 400 c.c. of concentrated blood of group A, Rh<sub>0</sub> Rh' without a transfusion reaction. During the first eighteen hours in the hospital he passed dark urine five times, the volume varying between 20 and 60 c.c. on each occasion. The urine hemoglobin content varied between 135 and 400 mg. per cent. All the dark urines contained both oxyhemoglobin and methemoglobin on spectroscopic examination. The icteric index, by the alcohol method was 10 and the quantitative hemoglobin in the plasma on admission was 120 mg. per cent. Both oxyhemoglobin and methemoglobin were present in the plasma. Kidney function was maintained for the specific gravity of the dark urines was 1.028 to 1.030. For the first eighteen hours in the hospital albumin was present in the urine and the urobilinogen titer was less than 1:10. About eighteen hours after the transfusion was started the urine became lighter in color. The albumin content diminished and finally disappeared. As the urine became lighter the urobilinogen titer rose from 1:10 to 1:80 and hemoglobinuria disappeared.

Twenty-four hours after transfusion the red blood count was 3.88 million and the hemoglobin was 10 Gm. Two days after transfusion the hemoglobin was 11 Gm. and the reticulocyte count was 2 per cent. The patient was discharged on the fifth hospital day with a hemoglobin of 10 Gm. and a red blood count of 3.85 million.

CHAIRMAN.—Dr. Stats, would you like to comment on this case?

DR. STATS.—This case is a typical example of a relatively mild hemoglobinuric episode of unknown causation which, while rare, is much more often encountered in early childhood than at other periods of life. In our experience such disorders are transient and recovery is to be anticipated after one or several blood transfusions. We have not encountered transfusion reactions in any unusual frequency in such cases if properly grouped and matched blood is given. We believe that the occurrence of hemoglobinuria and/or hemoglobinemia is a contraindication to splenectomy. Upon this finding alone we would divide hemolytic anemias into those in which splenectomy is valueless and those in which it may prove successful in bringing about a prompt cessation to excessive hemolysis. In acute idiopathic hemolytic anemia with hemoglobinemia the duration of rapid blood destruction is generally short-lived, lasting for four or five days. Once hemoglobinuria disappears it is not likely to reappear. Blood regeneration may be slow for a period as long as one month before restitution to normal in the blood figures occurs. Recurrences are rare.

DR. KARELITZ.—Dr. Schifrin, would you tell us what is concentrated blood?

DR. SCHIFRIN.—The concentrated blood used in this case was made by removing 100 c.c. of plasma from 500 c.c. of citrated whole blood.

DR. KOHN.—Was a Wassermann done on this patient?

DR. SCHIFRIN.—The mother had a negative Wassermann during the third trimester of this pregnancy.

DR. BLUMENTHAL.—How is the heat resistance test done and what is its significance?

DR. STATS.—The heat resistance test is performed by allowing the patient's blood to clot and remain at 37° C. for six hours. The presence of gross hemoglobin in the serum is a positive result and definitely indicates the presence of paroxysmal nocturnal hemoglobinuria.

DR. REUBEN.—Does blood serve as a replacement or does it in some way stop the hemolytic process in this disease?

DR. STATS.—That is a very difficult question to answer. It is probable that the blood acts only as replacement. In one case I observed, hemoglobinuria was diminishing before the blood transfusion was given.

DR. KARELITZ.—How does this differ from paroxysmal hemoglobinuria and why could this not be the original episode in a case of paroxysmal hemoglobinuria?

DR. STATS.—There are three types of paroxysmal hemoglobinuria: (a) syphilitic paroxysmal cold hemoglobinuria which was excluded by the negative Donath-Landsteiner test and absence of clinical evidence of syphilis; (b) hemoglobinuria due to cold hemagglutinins excluded by the low titer of cold hemagglutinins; (c) paroxysmal nocturnal hemoglobinuria excluded by the negative heat resistance test.

In summary, this 23-month-old male child developed an episode of severe hemolysis with hemoglobinuria and methemoglobinuria, and jaundice in the course of an infection, follicular tonsillitis. The process stopped after a transfusion of 400 c.c. This is considered to differ from paroxysmal hemoglobinuria by having a negative Donath-Landsteiner, negative heat resistance tests, and a very low titer of cold hemagglutinins.

#### Case 4. Mercury Poisoning

DR. RICHARD N. REUBEN (Assistant Resident in Pediatrics).—The patient was a 5-year-old white girl who was perfectly well until she swallowed a 0.5 Gm. tablet of bichloride of mercury. At the time of the mishap, the patient and her family were living in rural upstate New York, in a large house of which only a portion was in constant use. The child had been wandering one morning through the unused section when she discovered a bottle left on a shelf and swallowed one of the characteristic blue coffin-shaped tablets of mercuric chloride it contained. (The bottle was labeled "Poison.")

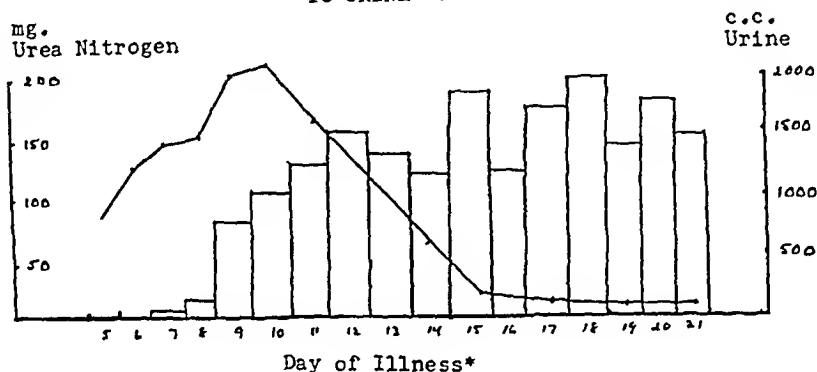
The patient soon afterward complained to her mother of a peculiar sensation in her mouth and the mother, on eliciting the story and identifying the bottle, gave the patient some milk and egg yolks. This was promptly vomited, the vomitus also containing some blood-streaked mucus and a small portion of the tablet. Because of persistent vomiting for about four hours, she was taken into town to see the doctor, who referred her to a second physician. Frequent small feedings of milk, repeated small tap water enemas, and sedation were prescribed. The child, however, continued to vomit and the enema returns were tarry and mucous-containing. Toward the end of the day she developed a diarrhea consisting of loose, green-black, mucus laden stools, but during the first day she apparently voided normally.

On the following day because of the recurrent vomiting and diarrhea, she was hospitalized in a nearby city. She voided a small amount of urine in the morning but was anuric for the remainder of the day. The next day, because of inability to retain oral feeding, she was given a clysis. The vomiting ceased and the diarrhea slackened. The patient remained anuric, and for the first time seemed lethargic. On the fourth day, parenteral fluids were given intravenously and by clysis (amount and type not known). The anuria persisted. BAL was administered in dosage described by attending physician as usual therapeutic amount. The lethargy seemed more pronounced although the patient seemed in generally good condition, and at this point the patient was transferred to the Mount Sinai Hospital where she arrived on the fifth day of her illness, having been anuric for about three days.

On admission the patient appeared listless but in no distress. The face was puffy. The skin turgor was good. The tongue borders were gray with tiny ulcerations and the mucous membranes of the mouth were red and slightly edematous. The pharynx was mildly injected. The lungs were clear and the heart appeared normal. The abdomen was soft and nontender. The kidneys were not felt and there was no costovertebral angle tenderness. Extremities

were normal. Blood pressure was 110/72, pulse 100, respirations 35, hemoglobin 8.1 Gm., and hematocrit 21 per cent. White blood count was 12,500, polymorphonuclear cells 77, lymphocytes 23. Blood urea nitrogen was 79, CO<sub>2</sub> content 34 volumes per cent, creatinine 17.7, uric acid 7.3, calcium 9.7, phosphorus 4.7, sodium 132 meq., chloride 90 meq., total protein 5.1 per cent, cholesterol 170 mg. per cent, Wassermann negative, ECG no abnormality.

CHART SHOWING RELATION OF BLOOD UREA NITROGEN LEVELS  
TO URINE OUTPUT



□ Daily urine volume in cubic centimeters.

— Blood urea nitrogen in milligrams per 100 c.c.

\* Patient entered Mount Sinai Hospital on fifth day of illness. History indicated that patient had voided normally on first day, then had been oliguric on second day and anuric on third and fourth days.

Chart 1.

The patient was placed on a regimen of restricted fluid intake consisting of 300 c.c. of sweetened fruit juices daily, the amount subsequently varying with gain or loss in weight. One hundred and fifty thousand units of Procaine-Penicillin were given daily prophylactically. The child remained lucid and comfortable, and sat up in bed. She took fluids poorly and continued to have watery brown stools for a week. She remained anuric for two more days or a total of five days. There were two succeeding days of oliguria (less than 125 c.c.) and then on the fifth hospital day or eight days after the onset of oliguria-anuria, the urine volume returned toward levels of 1,000 to 1,500 c.c. daily. Coincident with the return of increased urinary output the patient lost ten pounds over a period of a week. The urine at first was of low specific gravity (1.010 to 1.012) and contained occasional granular and hyaline casts and occasional white blood cells, but at the time of discharge, two and one-half weeks later, the sediment was negative and the specific gravity had risen to 1.020 on concentration test. Meanwhile the blood urea nitrogen had risen to

a high of 222 mg. per 100 c.c. on the tenth day of the illness but declined rapidly reaching normal levels by the sixteenth day. There were no significant changes in the carbon dioxide content of the blood.

With the return of urinary flow, the remainder of the course was uneventful. As the urine volume increased, the intake of oral fluids was raised so that it approximated the loss of fluid in the urine. The sodium chloride content of the urine was also measured, and an attempt was made to insure adequate replacement in the diet. During the first week of diuresis, the patient lost between 1 and 3 Gm. daily and salt in about the same amount was added to the food tray (on bread and butter, in tomato juice, etc.). The patient had some transient difficulty in retaining solid foods and the stools continued to have excessive amounts of mucus for about two weeks after onset of illness. Because of an anemia of 6.0 Gm. of hemoglobin occurring at the end of the third week of illness, the patient was transfused and thereafter maintained a hemoglobin over 10.0 Gm. The blood pressure, fundi and other physical findings had remained normal throughout the illness.

#### DISCUSSION

DR. ANFANGER.—How does BAL act in mercury poisoning?

DR. R. N. REUBEN.—BAL or British Anti-Lewisite is a compound containing two sulfhydryl (-SH) groups. Experimentally it has been shown that arsenic, mercury and other heavy metals produce toxic effects in the body by combining with the sulfhydryl groups of body protein and that BAL competes successfully with the protein to combine with the heavy metal. Although BAL may actually absorb some of the heavy metal already combined with protein, it is much more efficacious to provide BAL before the heavy metal has a chance to combine with body protein. Consequently the best results are obtained where BAL is given early, especially within three and one-half hours. It is given as a 10 per cent solution in peanut oil intramuscularly, and an accepted regimen is to give 5 mg. per kilogram of body weight initially, repeating a dosage of 2.5 mg. per kilogram at 1 to 2, 2 to 4, and 6 to 12 hours the first day. On the second day 2.5 mg. per kilogram is given twice and thereafter once daily for two or three days.

DR. KOHN.—Dr. Mann, you had an opportunity to study a series of cases of mercury poisoning some time ago. Would you discuss some of the methods used in treatment and the results obtained?

DR. L. T. MANN.—I had occasion to collect thirty cases of mercury bichloride poisoning from the records of Mount Sinai Hospital admissions from 1914 through 1935.

Three patients had renal decapsulation, and twenty-seven were treated medically by: (1) Attempting to immobilize the mercuric ion with sodium thiosulphate or sodium formaldehyde sulfoxylate, which is a reducing agent; (2) Eliminative treatment as gastric lavage, colon irrigation, and intravenous fluids; (3) Alkalinization and forced fluids; (4) Patterson-Lambert method

which consisted of 8 oz. of milk given every two hours, alkali by mouth, and colon irrigations.

All the patients vomited after taking mercury bichloride so that the amount retained and absorbed could not be estimated in any case. It should be emphasized, however, that the patients who took only one or two tablets, 0.5 to 1.0 Gm. all survived, whereas mortality was seen when 1.5 Gm. or more were ingested.

There were twelve male and eighteen female patients. The ages were from 13 years to 64 years, but the greater majority were in the 20's.

Seventeen took from 0.5 to 1.0 Gm. and, as mentioned, all survived. Twelve took from 1.5 to 3.0 Gm. of whom five survived and seven died. One other patient took 20 Gm., and the outcome was fatal.

In three patients, all female, a bilateral renal decapsulation was made. All of them died. They were anuric for at least three days. We found references to 203 patients who had ingested mercury bichloride and in whom a renal decapsulation had been made. There was a mortality of over 90 per cent.

The duration of the anuria in the fatal cases was from three to eight days. In two children that recovered one was anuric for three days and the other for ten days.

We have had a long follow-up of over ten years on five of our patients. They now all have normal urine and normal kidney function.

DR. J. KOHN.—Dr. Kroop, would you discuss the general management of the renal insufficiency seen in mercurial poisoning?

DR. I. G. KROOP (Dazian Foundation Research Fellow in Medicine).—The chemical and anatomical changes characterizing the acute renal insufficiency of acute mercurial intoxication are reversible. Despite the fact that mercury injures chiefly the proximal portion of the nephron, the disturbances of body equilibrium secondary to the acute uremia of mercurial nephrosis are similar to those of lower nephron nephrosis.

The treatment of the reversible renal insufficiency of mercurial nephrosis is similar to that described for management of renal insufficiency produced by hemoglobinuria. (Kroop, I. G., Fishman, A. P., Leiter, H. E., and Hyman, A.: The management of acute renal insufficiency following transfusion, to be published.) In the case of the latter, management resolves itself into the therapy of three periods: (1) the immediate emergency period following hemolysis; (2) the period of oliguria and anuria; and (3) the period of diuresis and beginning convalescence. This division is applicable to the treatment of mercury nephrosis. The emergency period in acute mercury intoxication requires the treatment of shock if present, and the energetic emergency measures toward the elimination and neutralization of the mercury which is a protoplasmic poison. Immediate effective therapy, as applied in this case, will prevent severe renal damage and will shorten the period of oliguria and anuria. Gastric lavage with protein containing fluids precipitates the mercury.



Colonic irrigations remove the mercury which is excreted into the large bowel. Continued lavage and irrigation beyond the immediate emergency period is not advisable because it might lead to electrolyte and water depletion. BAL (2,3 dimercaptopropanol) should be administered in full dosage within three and one-half hours after the ingestion of the mercury bichloride. It should always be given, even if begun as late as twenty-four or forty-eight hours after ingestion of mercury. BAL combines with mercury, detoxifies it, and aids in its excretion.

The principal aim of therapy during the period of oliguria and anuria of the acute renal insufficiency due to mercury, is the maintenance of fluid, electrolyte, and acid-base balance. Fluid and salt restriction is imperative during this period. Excessive fluid administration will not initiate urine flow and may lead to cerebral and pulmonary edema. Acidosis, if clinically significant should be corrected with alkali by mouth. If alkalinization of the urine is difficult it should not be attempted since it may lead to severe alkalosis. The guiding therapeutic principle in this second period of oliguria and anuria is to prolong the patient's life long enough for tubular regeneration to occur and for diuresis to herald recovery of function. If despite proper management the condition of the patient deteriorates, an artificial means of dialysis may serve as a useful therapeutic adjuvant. Peritoneal lavage (Frank, H. A., Seligman, A. M., and Fine, J.: *Treatment of Uremia After Acute Renal Failure by Peritoneal Irrigation*, J. A. M. A. 130: 703-705, 1946), and extra corporeal dialysis of blood with an artificial kidney (Fishman, A. P., Kroop, I. G., Leiter, H. E., and Hyman, A.: *Experiences With the Kolff Artificial Kidney*, to be published) are the most efficient methods available. These methods, however, are not a substitute for correct medical management.

The aim of therapy during the period of diuresis and beginning convalescence is the maintenance of fluid and electrolyte equilibrium. The loss of excessive quantities of water and salt in the urine may lead to dehydration, acidosis, and recurrent oliguria. Salt retention instead of salt loss may occur in some instances of tubular dysfunction. Under these circumstances, administration of sodium chloride and fluid may lead to pulmonary and cerebral edema. It is clear that chemical determinations of chloride in the blood and urine are essential guides for proper therapy.

This case of acute mercurial nephrosis in a five-year-old girl with complete anuria for five days, and oliguria for three days, illustrates the application of these principles of therapy. Pulmonary and cerebral edema were avoided by restriction of fluid and electrolyte. Dehydration was prevented during the period of diuresis, which began on the ninth day. At no time was there any indication for the use of the artificial kidney. Meticulous medical management, according to the principles outlined above, led to an uneventful recovery.

DR. KARELITZ.—Dr. Sirota, this patient had a renal vein catheterization and kidney function studies just prior to discharge. Would you discuss your findings?

DR. J. H. SIROTA.—The results of the renal function tests performed on the twenty-second day after onset of anuria are tabulated below. The values are based on the clearance techniques of Homer W. Smith.

All figures are corrected for an ideal surface area of 1.73 square meters.

## PLASMA CLEARANCES\*

	INULIN (C.C./MIN.)	PAH (C.C./MIN.)	T <sub>m</sub> PAH (MG./MIN.)	CIN/ T <sub>m</sub> PAH	C <sub>PAH</sub> / T <sub>m</sub> PAH
Twenty-second day from onset of anuria	78.2	236	28.8	2.72	8.22
Normal values	117	594	82.2	1.42	7.25

\*T<sub>m</sub>, Maximum tubular excretion.

PAH, P-aminohippuric acid.

C<sub>PAH</sub>, Clearance of P-aminohippuric acid.

CIN, Inulin clearance.

The inulin clearance is usually accepted as the glomerular filtration rate and the PAH (P-aminohippuric acid) clearance as the renal plasma flow through functional renal parenchyma. However, these figures must be interpreted with caution when applied to severely damaged kidneys (Notes on the interpretation of clearance methods in the diseased kidney, Smith, H. W.: *J. Clin. Invest.* 20: 631, 1941). Thus, the above value for the PAH clearance of 236 c.c. per minute/1.73 sq. m. cannot be accepted as the renal plasma flow unless it can be shown that under the conditions of the test about 99 per cent of the PAH is removed from the blood during one passage through the kidney. This can only be ascertained by simultaneous sampling of the arterial and venous bloods by renal vein catheterization and arterial puncture. Unfortunately, this was not done with this patient.

The subnormal figures obtained for the ability of the tubules to secrete PAH at high plasma levels (T<sub>m</sub>PAH) reflects severe functional damage to the proximal convoluted tubules.

Endogenous creatinine clearances performed on the tenth and fifteenth day of the disease were 4.03 and 4.07 ea per minute respectively. Since the clearance of the substance has been shown to approximate glomerular filtration (The renal clearance of endogenous "creatinine" in man, Brod, J., and Sirota, J. H.: *J. Clin. Invest.* 27: 645, 1948), one must assume severe depression of this function or considerable back diffusion of glomerular filtrate through damaged tubular walls. Thus, the anuria and oliguria of this disease may be explained by decreased glomerular filtration and/or marked tubular back diffusion of formed glomerular filtrate.

The elevation of the ratio C<sub>PAH</sub>/T<sub>m</sub>PAH suggests that the tubule cells which are functioning in the proximal convolution are receiving an adequate blood supply.

From past experiences, one may predict the return to normal, in several months, of all functions tested. The inulin and PAH clearances return to normal first, being followed by the T<sub>m</sub>PAH and finally by the ability to maximally concentrate urine.

# Psychologic Aspects of Pediatrics

## HOW CAN NURSERY SCHOOL BE EXPECTED TO BENEFIT A CHILD?

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IF THE conditions are auspicious, nursery school experience can be a salient factor in starting a child on the road to healthy growth and development. It cannot, however, be taken for granted that every nursery school will have positive value for every child. The decision as to whether a particular child shall go to nursery school, and the choice of the school, needs discriminating consideration in terms of (1) the maturity of the child and his readiness to be separated from the home, (2) the nature of the home situation which would be alternate to his attending a nursery school, (3) the qualifications of the staff of the nursery school to meet the growth needs of young children and to handle the special problems which arise when young children spend long periods of time together, (4) the physical set-up of the nursery school and its health standards, and finally, (5) the question as to whether the experience will contribute to the basic happiness of the child.

There are many occasions when the pediatrician is involved in this type of decision. This paper will present, from the point of view of the psychologist, a brief digest of the potential influence of nursery school experience on the development of the child.

### PSYCHOLOGIC DEVELOPMENT DURING THE NURSERY SCHOOL YEARS

It is during the period of early childhood that the child becomes aware of himself as apart from other people and lays the foundation for attitudes toward himself as an individual. His energies and curiosities bring him into throbbing contact with his environment and in his pattern of responding to these stimuli he is developing attitudes that will have an important effect on his role as a working adult. He faces the dilemma of getting his fill of love and protection and at the same time weaning himself from the infantile dependence which becomes emotionally irksome as his skills, his assertiveness, his individuality all begin to blossom. He needs a basis for differentiating one sex from another, identifying himself with his own sex, and, for the sake of his future happiness in sex and family relations, feeling content with his membership in his own sex. He is formulating his role as a child to his parents and, implicitly, laying the groundwork for the kind of parent he will be to his own children.

He struggles with adapting his own impulses to the requirements of civilization in many guises—toilets, forks, neatness, money, etc. In his long hours of play with other children he is establishing a *modus vivendi* for living with

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other people. He encounters specific forms of restraint and authority and, out of the wide range of possible reactions to authority—cringing, anger, subterfuge, resentment, acceptance—he develops an individual formula compounded of his own temperamental qualities as well as the quality of authority which he experiences. He experiences denial, frustration, loneliness, fear, pain, anger, and out of all this emotional weathering his own style of endurance and feeling begins to take shape.

#### TECHNIQUES AND EQUIPMENT IN THE NURSERY SCHOOL

The nursery school, as an educational institution, has an important function in helping young children come to grips with these major life-problems of their early years. This is accomplished partly by the program of activities in which the children engage and the experiences which are provided for them. More important, however, is the psychologic atmosphere engendered by the adults in the school and the adequacy of insight and training which they bring to this highly specialized task. This psychologic atmosphere consists of certain basic attitudes such as the acceptance of the child as a person rather than the censorship of his behavior, interest in ascertaining the motives behind his behavior, awareness of the back-and-forth nature of growth, and facility to nourish the first signs of independence without rejecting the child's lingering need to be supported and protected. These general attitudes determine the quality of the experience which the child derives from his activities. They underlie the specific techniques which the teacher uses in connection with various aspects of the program.

Typically, the young child makes a physical-motor attack on the things in his world, sometimes through manipulating small objects, at other times through putting his large muscles or his whole body into vigorous motion and action. The nursery school is set up to provide ample, varied opportunity for the child to enjoy his physical vigor and, incidentally, to learn the nature of the physical objects in his surroundings. Slides, parallel bars and ladders, jungle gyms, see-saws, wagons, triicycles, scooters, large hollow wooden blocks, kegs, and brooms are part of the standard equipment, located usually outdoors, which is an essential prerequisite for adequate nursery school housing. A group of young children in contact with these objects spontaneously engages in a repetitive round of sliding, swinging, climbing, hanging, balancing, rolling, steering, heaving, pushing, stacking, and dragging. The benefits to development of muscular strength are obvious. There are, in addition, less obvious but more significant psychologic values. Instructions and restrictions are minimal, and limited to safety needs: the child is thus left free to explore, to experiment, to invent, and to discover. He is free from the host of prohibitions imposed upon him when he lets loose his most active impulses at home. In the course of physical activity, he encounters and comprehends more and more complex concepts of physicospatial relationships, "high and low," weight and pressure, wheel and axle, hoisting, leverage, etc. He is free from influences to use things as manufacturers conceive them, or as seem fascinating to his father. The child, then, has not only the pleasure of varied physical activity but also the delight of

making independent discoveries and the experience of impressing his own individual pattern on the environment.

In giving the children wide opportunity for action and expression and a minimum of prescribed instructions, the nursery school faces and takes certain specific responsibilities. Planning for space, equipment, and materials has to weigh carefully differences in age and capacity at different levels of the nursery years. Otherwise, the possibilities for accident and frustration are too great. No matter how carefully planned, there will be in any group of children incidents of reluctance, fears, frustrations, and of minor injuries. These themselves may constitute growth experiences when the child can feel confident that the teacher is competent to care for his injury and will express sympathy for his pain, that she will gladly stand by when he is slowly getting up his courage to step up to the highest rung, that she will be at hand to help undo the terrible tangle of rope that keeps the wheels from going around, that she will not make him feel he is a coward because he does not like to swing as high as the others do.

There is another kind of material which is provided plentifully for the children's spontaneous creative uses. This consists of colored paints, crayons, plenty of blank paper, building blocks, scraps of cloth, finger paints, modeling clay, anything, in short, which the child can manipulate, mould, or combine according to his own ideas. Left to his own devices, again with only a few restrictions as to ways in which materials may not be used, the child is free to enjoy the pattern of color which he devises or the structure of blocks which he erects. The opportunity to create according to his own impulse has several kinds of value to the growing child. In his private, independent experiences with color, design, or construction, the child is establishing himself as an individual capable of original creation; this is a process that is basic to his healthy ego development.

Through creative expression he can also release some of the pent-up, intense feeling generated in the course of his everyday life as a relatively helpless child in a world of powerful, all-knowing adults. In recent years, the value of free creative expression for young children has been clearly recognized since studies of their free products have demonstrated a detailed and close relation to the emotionalebb and flow of their lives. To assure these psychologic benefits to the child, more than the materials for creative expression are required. The teacher needs to be sensitive and appreciative of the children's products in terms of what the experience means to them. She does not apply extraneous standards of neatness, correctness, or photographic resemblance. She accepts the products as she does the child, careful not to impose adult criteria where they do not belong.

#### VALUE OF SOCIAL CONTACTS AND PLAY

It is not usually for these values, however important we may consider them to the child's developing individuality, that nursery schools are sought out by parents. It is more likely to be in search of companionship for a child who is lonely or bored, and therefore troublesome. Opportunities for playing and living together in nursery school are directly and deeply exhilarating, and the

children's joy is often eestatie in quality. Besides this direct pleasure in soeial contacts with other children the young child in nursery school has a ehance to widen his sphere of identifieation. He now belongs not only to the family into which he was born but to his school, a soeial group outside the home, and he is gradually initiated into the eomplicated soeial proecess by which individuals maintain themselves as aeeceptable and wanted members of soeial groups. Slowly he learns the mores of the nursery group: how to wait turns, the need to surrender what one does not use, how to settle conflicts by agreement and arrangement rather than fists, how to adjust his impulses to the requirements of the soeial situation.

He can count on the teacher to find an imaginative and just solution for the struggles, to exaet no greater yielding of his own impulses than is suitable and healthy for his age and temperament, to be patient in repeated explanations and reminders, to join herself, from time to time, in the deeper experiences of kinship.

The children's life together in a nursery school constitutes primarily a life of play. In a spontaneous flow of ideas and aets, they play out dramatically the salient experiences of their lives, weaving the sequence as they go, shifting roles and changing scene without too much regard for the demands of logie and reality. This free dramatic play serves a variety of functions. Real experience is deepened and clarified as it is lived through dramatically over and over again. Much of the play however is symbolie in character or has symbolie elements through which the child uneonseiously expresses anxieties, fears, wishes that he cannot deal with directly. The value of play in eonnection with emotional disturbance is being demonstrated currently in the growing use of play therapy as a technique for working with deeply disturbed children.

The teacher maintains an apparently passive role in relation to the children's dramatic play although she may become a participant on oceasion by invitation. Her role, however, is not as passive as it appears on the surface. From her observations of the children's play she is guided in her dealings with individual children and their special problems. She also senses when the children as a group are ready for more extended experiences. The play of the children emerges in large measure from their experiences as members of families. It is also constantly nourished by the teacher's carefully planned program of trips into the neighborhood, reading of stories, and diseussions of common experiences through which she develops the children's sensitive awareness and understanding of the world around them.

Briefly, one might summarize the values of nursery school experience which have been referred to so far by saying that they enrich the life of the young child, bringing to greater fulfilment the impulses which are natural to him at this stage of his development. Further, it has been indicated how important are the attitudes surrounding these experiences in relation to his growing sense of ego, his extended kinship feelings beyond the limits of home and family, the development of his creative and expressive capacities, his confidence in his own ability to discover, invent, and solve problems, his indirect resolution of emotional problems through symbolized dramatic play.

## DISCIPLINE IN THE NURSERY SCHOOL

In the nursery school, then, he finds stimulation, understanding, heightened pleasures, and a great measure of freedom to grow through untrammelled expression of his feelings and interests. Just as vital to his total growth is his experience with control and authority. A child's mental health is conditional not only upon being loved, accepted, and protected but also upon having reasonable limits put upon his behavior, upon being stopped from carrying to excess some of his impulses (to be aggressive, for instance) and upon being able to accept certain decisions which must be made for him and cannot always be comprehensible to him. One of the goals of the nursery school is to give the child experience with temperate authority in contrast to the absolutism that was formerly characteristic of relations between adults and children.

In application, the concept of temperate authority refers to concrete ways of dealing with children. Severe punishments such as hitting, shaming, ridiculing, frightening are never visited upon the child. The teacher does not attempt to overpower him. Instead she makes an effort, as far as feasible, to let him know the reasons for what is expected, what is restricted, and what is not permitted. She tries to diffuse authority by having her student teachers and assistants share it and by having some of it implicit in the way she arranges schedules and programs until the children come to see what the situation requires. In exerting authority, it is the behavior which she censors and rejects, not the child. The child, in accepting this kind of discipline and authority, is neither humiliated nor demeaned. The value of experiencing authority of this kind while basic personality is still in formation extends beyond the sphere of the mental health of the child. It constitutes a psychological bulwark for a democratic society.

In the development of these goals and practices during the last thirty or forty years the nursery school has been part of a larger educational movement usually referred to as progressive education. The progressive school has outlived its early experimental period and, we trust, is fast outliving some of the misconceptions concerning its practices and intentions. The concepts of fulfillment of the individual, the importance of motivation as a basis for efficient learning, of freedom without license, of learning through activity and direct experience, are only some of the tenets which are being absorbed currently into the practices of all modern schools, both public and private. The term "progressive" no longer refers to a small group of pioneer institutions. In fact, as a term, it is used less and less as its basic ideas are becoming the criteria by which we judge all good schools.

The attitudes concerning growth, freedom, and discipline, which have been attributed to teachers in nursery schools in the foregoing sections, are coming to be more and more characteristic of the relationships between parents and children. The question might be asked whether this does not make the nursery school experience superfluous. Certain features of nursery school are distinct from those of the home. For the sake of the child's wholesome growth as a psychologically independent individual there is great value in his realizing as early and as deeply as possible that the world outside the home and family holds

a full measure of warmth and security, great possibilities for pleasure and accomplishment. For some of the specific problems of his emotional development the nursery school has a distinct contribution to make just because his teachers, though intimate and close to him, are not as emotionally involved with him as are his parents, because there are children to enjoy with whom he does not have to work out sibling relationships, because the stage can be set for his childish interests and activities without interfering with the needs and preferences of adult living. For many children there is healthy satisfaction, also, in the expanded opportunities for achieving skills that add to one's feelings of independence and, more than that, an emerging sense of having a life of one's own.

#### THE DIFFICULT CHILD

Briefly outlined, these are the values for *any* child which are inherent in good nursery school education.\* For the children who have more than the usual share of difficulties in early childhood, the experience can have important therapeutic value. The training of the teacher equips her to observe the child and study his behavior in order to understand its meaning, to provide a program of interests, and to guide his relationships according to his special needs and problems.

The behavior of the child is only the first clue to his difficulty and the teacher can plan intelligently only when she has studied the child sufficiently to have a tentative hypothesis as to the causes underlying his behavior. For example, a child may behave with extreme diffidence and hesitation when he comes to school, for any number of different reasons. His shyness may be due to the fact that he has made very few close relations to adults outside of a small family circle, or that he had been dominated and directed by an older sibling and felt at a loss as to how to act independently, or that he comes from a family of people who are naturally slow-moving and quiet and consequently he finds the nursery school atmosphere overwhelming rather than exhilarating at first. He may not speak the language of the children in the group, literally or figuratively, or he may be by nature one of those people who warm up slowly to all new situations.

Relieving his shyness is not a straightaway problem. The teacher may need to keep him close by her side through the early days until, having found confidence in a close relation with the teacher, he gathers strength to try himself out in contacts with the children. She may try to discover some special interests or experiences that he has, through which she can help him become interesting to the group. A cracker, a piece of toast, an extra dessert can help to break the ice when words might fail. Some children need only to be left to their own devices and allowed to stand quietly watching without partaking. Others take avidly to using all the materials and objects and gain their ease through becoming familiar with what there is to do before they can plunge into

\*Printed pamphlets and articles on all aspects of nursery school education are available through National Association of Nursery Education Distribution Center, Roosevelt College, 5 Michigan Ave., Chicago, Ill.; Association for Childhood Education, 1201 16th Street, Washington, D. C.; New York City Committee of Mental Hygiene, 105 East 22nd Street, New York, N. Y.; The Bank Street Schools, Division of Research and Publications, 69 Bank Street, New York, N. Y.



social contacts. In some instances the teacher may realize that only through working with the family will she be able to help a particular child over his reluctance to take part in the life of the group.

What is true generally for shy behavior is also true for aggressive behavior, for bullying or whimpering, or for cheating or stealing on older age levels. There are no ready formulae for how to deal with these children or with others who may be especially fearful, anxious, rebellious, or sluggish. The details of the techniques to be applied have to be arrived at after each child's problem is studied and understood in terms of his personality and his total life situation. The extent to which they will be successful will depend on the depth of insight, the imaginative skill, and the emotional maturity of the teacher herself.

In any case, it is important to remember that the behavior difficulties of children who attend nursery school are relieved not only because of the specific techniques which the trained teacher knows how to use but also because of certain qualities pervading the entire situation. Among the most important are the teacher's acceptance of the child as a person despite the difficulties he may cause and the relief of working through one's problems in a nonfamily setting. For all these reasons, nursery school experience can be a valuable therapeutic agent, when there are not too many and too serious factors in a child's total life-situation operating against healthy resolution of problems.

#### INDICATIONS FOR NURSERY SCHOOL ATTENDANCE

We may return to the question posed in the beginning of this discussion concerning the points to be considered in coming to a decision as to whether a child should go to nursery school. Not all nursery schools are set up or equipped, nor all teachers trained in a way to offer this experience to young children. For some children a less than perfect nursery school may still be of great benefit. There are children whose home situations cannot provide what they should have of minimum essentials—space to move about in freely, a period of outdoor play each day, things and experiences through which to develop their growing bodies and minds, children to play with, and an atmosphere in which to have fun and be happy. There are children whose mothers work and leave them poorly provided for. There are children of professional women left in the care of domestic servants. There are children of broken families. In cases such as these, the decision to send a child to nursery school, even one which may not be achieving the highest possible standards, must be made in practical terms, by weighing and considering what his alternative environment would be. For judgments of this kind to be made with fewest possible errors it is important that there should be more widespread knowledge and understanding of the basic principles of nursery school education.

Decision to send a child to nursery school is a matter of *when* as well as *if*. In educational circles there is doubt and disagreement as to whether the nursery school should be set up for 2-year-old children, even though a considerable number of good schools have had many years of successful work with children in this age group. The issue will be difficult to resolve since it is bound up with differences in individual rates of development. Some 2-year-olds seem

to thrive in the nursery school situation. These are the children who are developmentally ready for long periods of separation from home and family, whose verbal and muscular skills are far enough along to keep them from feeling overwhelmed, who have enough stability to be able to carry on their bodily functions in a strange setting without being too deeply disturbed, and who have already developed a need for continuous contacts with other children. However, for many, this transplanting constitutes considerable strain.

The experienced staff member of a nursery school, after an interview, a home visit, and a little time with the child, is usually able to predict what the 2-year-old's reaction will be. With these very young children, there is more need for hesitation and careful consideration than is true for the 3-year-old. However, at any level in early childhood, leaving home and going to school for the first time is a stirring, often a shaking, experience. Practice now dictates that this period of weaning from home should be cushioned for the child as much as circumstance permits. Mothers are persuaded to remain in school while the child is getting initiated and gradually becoming familiar and secure. In some cases, it is best for the child to stay only for short periods in the beginning and it may be a matter of weeks before he is ready to spend a full day and take the round of eating and sleeping away from home.

In concluding, it should be noted that the value of the nursery school to the child depends not only on how good the nursery school is or on how inadequate his home is, but also on the motive of the parents in sending the child to school. One mother may be motivated by her own feeling of inadequacy, another by the wish to provide the best possible care and still another by a desire to reduce her own responsibility to a minimum. These differing motives will affect the child's receptivity to the nursery school experience. Because of his knowledge of the mother's personality, the pediatrician is in a favorable position to take this factor into account when his advice is sought.

# The Social Aspects of Medicine

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## THE EWING REPORT

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ON SEPT. 2, 1948, Federal Security Administrator Oscar R. Ewing submitted to the President a report entitled *The Nation's Health—A Ten Year Program*. This report was in response to a request of the President made in January of that year. In May, 1948, Mr. Ewing called together the National Health Assembly, reports of which have been presented in various journals and need not be discussed at this time. The Ewing report draws heavily upon the material from that assembly and the discussions of the various sections, following in large measures its recommendations but departing from them in some respects, particularly with regard to compulsory health insurance, about which the assembly took no definite stand. The report is long and cannot be condensed into a few pages; it is worthy of careful reading by all members of the medical profession for, in view of the recent election results, it is probable that it will form the basis for legislation introduced into the next Congress. I should like to review briefly its main provisions without agreement or disagreement except in a few instances, and then only in most general terms.

The report begins with a blunt statement of some of the deficiencies in our national health record and the importance of doing the "utmost to insure that all the people everywhere attain the highest possible level of health." It then states the types of services and care that are needed to attain this goal. As listed, they are (1) medical and dental care, (2) a healthful community, (3) a community clinic, (4) a community hospital, (5) a district hospital, (6) special hospitals, (7) a medical center, (8) coordination, and (9) a prepayment plan. Also listed are parallel needs of (1) rising standard of living, (2) better educational institutions, (3) increased benefits to the aged and disabled, (4) adequate housing, and (5) public education in relation to health. Attention is called to the difference between demand and need and the methods of measuring adequacy of providing for need in the field of health. With this background, the key problems to be met are: (1) manpower, (2) hospitals, (3) local organization, (4) research, and (5) individual cost of care.

There are two methods by which the nation may proceed to improve the health situation: to continue slowly, as has been done in the past, or "to strike out boldly but with careful planning to bring our health resources quickly into line with our national and individual needs." The author concludes "that more extensive and efficient nation-wide planning is the only effective way to accomplish a significant betterment in national health." The remainder of the report is concerned with an elaboration of the key problems mentioned above and the nationwide plan to solve the problems. The parts to be played by the Federal,

State and local communities are discussed and emphasis is placed upon the desirability of working from the community up, not from Washington down. Throughout the entire report there are many statistical statements, based upon surveys and reports, and some opinions based on personal observation. These will not all be accepted as exact in every detail, nor will one always agree with the inferences drawn from them, but, by and large, they present a true picture of conditions in the fields with which they are concerned. The cost of sickness and disability and the wisdom of investing money to prevent this loss are recorded as further arguments for the need of a national health program.

There is a full discussion of manpower, physicians, dentists, nurses and public health workers—and its importance to the health program. Attention is called to the uneven distribution of personnel and selective shortages in particular fields. This is in line with the material found in the Report of the Committee on the Costs of Medical Care made twenty years ago. It is estimated that there are only 80 per cent of the physicians needed and that at the present rate of increase there is no prospect of filling the gap. It is proposed to accelerate the increase by “expanding and establishing medical colleges and teaching hospitals” by the use of public funds. The difficulties in hospital finances are to be met also by assistance from the Federal Government, a beginning of which has been made through the Hospital and Survey Act of 1946.

There follows a presentation of the unequal chances for health, relating them primarily to differences in financial status and emphasizing the economic barriers to utilization of health resources and the delay in seeking medical care. The author concludes that unless this barrier is overcome “the Nation will continue to be seriously handicapped in its efforts toward better national health.” He then quotes the conclusion of The National Health Assembly’s Section on Medical Care, that “the principle of contributory health insurance should be the basic method of financing medical care for the large majority of the American people.”

The discussion on voluntary insurance plans calls attention to the good work which they have done and points out the obvious shortcomings, incomplete coverage and high cost. “The people who need health insurance most will not be able to get it under voluntary plans.” The rest of the report presents the plan of a government insurance program.

The Government plan, as presented, envisions four phases:

- Phase one: “Federal legislation to settle the basic policies of a system of government insurance and to decide important details . . . and to provide a three-year ‘tooling-up’ period before the date on which insurance benefits are made available.”
- Phase two: “The ‘tooling-up’ period during which procedures would be worked out cooperatively by professional groups, localities, States and the Federal Government.”
- Phase three: “Operations begin.”
- Phase four: “Expansion of services . . . until comprehensive services are available to everyone in the country.”

*Phase One, Legislation.*—Provision would be made for statement of objectives, coverage, premiums, benefits, guarantees to insured persons, professional freedoms, benefits for rural people, education and research, state and local administration, allocation of funds, Federal administration, and collections. In the discussion of *Professional Freedoms*, the statement reads:

“The law should give . . . explicit guarantees to the members of the professions who provide services, including the right to participate in the plan or not, to act individually or in groups, to accept or reject patients who choose them, to retain control of professional aspects of professional service, to choose the method of payment for services rendered, to negotiate rates or amounts of payment and other matters through representatives of their own choosing, to make complaints or appeals before appropriately constituted committees, and to turn to the courts for review of administrative decisions. Such guarantees would preserve the essential freedoms of the professions and assure that they could not be ‘regimented’ by administrative officers.”

The suggestions in relation to the other matters are quite specific but will not necessarily be embodied in the legislation which may be introduced into the Congress. Discussion of them may well wait until such time as a bill is presented for hearings and enactment.

*Phase Three, Operations.*—It is estimated that 60 per cent of the population would be covered by the plan at its inception, with the ultimate goal of 100 per cent. The basic services, physicians, hospitals, expensive medicines, and appliances, would cost probably 3 per cent of annual earnings up to \$4,800 a year, divided between subscriber and employer. When other services are added, an additional 1 per cent would be needed.

It is stated that the plan as outlined would make five fundamental contributions to better health:

“1. It would largely solve the individual’s problem of paying for medical care, and thus help encourage prompt care and preventive treatment.

“2. Because it creates a stable and assured financial basis for health services, it will generate effective demand and assure the fastest possible increase in our supply of medical manpower, health facilities and other essentials in all parts of the country.

“3. Because insurance will pay for a patient’s needs, doctors will be free to practice the highest quality of scientific medicine, uninhibited by the individual patient’s ability to pay out of personal income for all the diagnostic and treatment services, hospitalization and nursing care which professional judgment prescribes.

“4. Because insurance will abolish most of the financial obstacles to receiving medical care and help equalize community purchasing power, it will reduce the present large disparities in distribution of manpower and health facilities between lower-income areas and wealthier districts.

“5. Because national health insurance will furnish a new and badly needed opportunity for co-ordination of all community and regional personnel and facilities, it will help build a more effective organization for providing the best in prevention, diagnosis and treatment.”

There is next a section devoted to a consideration of six objections to Government health insurance:

"Briefly, the six arguments are these: (1) That Government health insurance is socialized or state medicine, (2) that it is compulsory, (3) that it would be highly centralized and would concentrate too much power in Federal Government, (4) that there are not sufficient personnel and facilities to make it effective, (5) that it would cost too much, and (6) that it would open the way to over-use and other abuses and would lower the quality of medical services."

Each one of these objections is met by factual material and opinions, leading the author to conclude that the adverse arguments are not conclusive, and that, in fact, the suggested plan effectively overcomes the difficulties about which the opponents are particularly apprehensive. This portion of the report ends with this sentence, "I, therefore, recommend that the President continue to urge upon the Congress the earliest possible enactment of government health insurance in some such terms as outlined in this report."

There are four chapters dealing, respectively, with mental health, the aging population and chronic diseases, the handicapped, and child health. Methods for improving present conditions and the part to be played by Government are discussed. There is nothing strikingly new with regard to child health. In general, it is advocated that the present services be expanded along present lines but made inclusive in those areas which are particularly backward.

The final chapter deals with community action. This is a clear presentation of the advantages of "effective team work for the welfare of the entire community." It outlines the generally accepted plan of rural clinics, local hospitals with district and base hospital communication. It calls attention to the importance of the medical school center and the advantages of group practice. The report ends with a plea for community action and team work:

"If the people will get together—professional workers and public representatives alike—in citizen health councils throughout the country, we will have the satisfaction of proving not only that health is everybody's business but that it is good business, essential business, and successful business."

## Comments on Current Literature

### CHLOROMYCETIN

THE antibiotic, Chloromycetin, obtained from strains of *Streptomyces* which were isolated from soil and compost,<sup>1-3</sup> is known to inhibit a wide variety of gram-positive and gram-negative microorganisms. These include *Bacillus subtilis*, *Staphylococcus aureus*, *Brucella abortus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella schottmülleri* and *Shigella paradyse enteriae*.

In addition to its effect on bacteria, Chloromycetin was shown to have a beneficial effect when administered to mice and to embryonated hen's eggs infected with a number of rickettsial agents or with viruses of the psittacosis-lymphogranuloma venereum group.<sup>4</sup> Noninfected control mice and embryonated eggs which received amounts of Chloromycetin comparable to the maxima used in the experimental series remain unaffected, indicating low toxicity of the drug. On the basis of early observations concerning low toxicity, ready absorption from the alimentary tract, and beneficial effect even when administered late in the experimental infection, Smadel and his associates<sup>4</sup> suggested that Chloromycetin might prove valuable in the treatment of patients. Subsequent clinical experiences have borne out their suggestion.

A preliminary study<sup>5</sup> was made on a group of volunteers who received maximum single or repeated oral doses, and in no instance were toxic manifestations observed during or after administration. Following this preliminary work on normal volunteers, five patients with typhus were treated with the same oral doses.<sup>6</sup> Improvement was noted in all five patients with fall in pulse rate and body temperature, and no toxic effects were observed. Subsequent opportunity for more extensive therapeutic testing<sup>7</sup> was afforded in cooperation with the Malaya Institute of Medical Research during an outbreak of scrub typhus at Kuala Lumpur. Twenty-five hospitalized patients were treated with Chloromycetin and at the same time twelve untreated hospitalized patients were observed. The results of these observations indicated that Chloromycetin had a favorable effect on the clinical course of scrub typhus.

In a recent issue of *Annals of Internal Medicine*,<sup>8</sup> Pincoffs, Guy, Lister, Woodward, and Smadel report their experience with Chloromycetin in the treatment of Rocky Mountain spotted fever. Fifteen cases confirmed later by laboratory findings were treated. Ten of these patients were under 16 years of age (2 to 16) and five were above this age (17 to 64). The dosage regime was empirical. The initial dose, which was administered per os in two or three parts at approximately one-hour intervals, ranged from 50 to 75 mg. per kilogram estimated body weight; in one instance 128 mg. per kilogram estimated body weight was given. After the initial dosage Chloromycetin was administered at three-hour intervals, 0.25 Gm. every three hours for children under 16 years of age, and 0.5 Gm. for those over 16 years of age.

While some improvement was noted during the first twenty-four hours of treatment, striking amelioration of the clinical manifestations was observed during the second day of therapy. "On the third day, in the majority of cases, the patient was plainly convalescent."<sup>8</sup> In all cases the temperature fell to normal levels within seventy-six hours after the initial dose. Other than occasional vomiting following the initial dose, no toxic manifestations were observed.

In the course of the investigations on scrub typhus in Malaya, the authors encountered numerous cases of typhoid fever which is endemic in this area, and which occurs in a severe form, the febrile course running from six to eight weeks. These cases offered opportunity for testing the value of Chloromycetin in this important enteric disease.<sup>9</sup> Diagnosis in the ten cases treated was confirmed by blood cultures positive for *Eberthella typhosa*. Beneficial effect of Chloromycetin was noted within the first twenty-four hours following administration in improved general condition of the patient and in lessened toxicity. The febrile course was reduced considerably. While the optimum schedule for the administration of the drug in typhoid fever remains to be determined, in this series the initial dose in each case was 50 mg. per kilogram of estimated body weight, then 0.25 Gm. administered every two hours until the temperature was normal, and 0.25 Gm. every three to four hours during the first five days of normal temperature. The total dosage averaged 19.1 Gm. over a period of 8.1 days. No clinical evidence of toxicity was observed.

The striking effect of Chloromycetin on the clinical course of epidemic typhus, scrub typhus, Rocky Mountain spotted fever, and typhoid fever indicates that this antibiotic is to date the most effective therapeutic agent available in the treatment of these diseases. The apparent lack of toxicity, the ease of administration by the oral route, the beneficial effect even when administered relatively late in the disease, and the broad coverage of therapeutic effectiveness make this drug an outstanding addition to the medical armamentarium.

RUSSELL J. BLATTNER

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## News and Notes

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Dr. Bert I. Beverly of Oak Park, Ill., died Sept. 27, 1948. He was associate professor of pediatrics at the University of Illinois and for years had been one of the leaders in the field of child psychiatry.

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Dr. John D. Lyttle of Los Angeles died Nov. 26, 1948. Formerly associated with the Columbia Medical Center and Babies Hospital in New York, he went to Los Angeles in 1944 where he was Medical Director of the Children's Hospital and professor of pediatrics at the Medical School of the University of Southern California.

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At the annual meeting of the *American Academy of Pediatrics*, held in Atlantic City Nov. 19 to 22, Dr. Warren R. Sisson of Boston was elected President for 1948-1949, and Dr. Edward B. Shaw of San Francisco, President-Elect.

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Dr. Milton J. Senn, professor of pediatrics in psychiatry at the Institute of Child Development at Cornell Medical College, has been appointed Sterling professor of pediatrics and psychiatry at Yale. He will be director of the new Yale University Child Study Center which will include the Yale Clinic of Child Development.

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Dr. Hunter H. Comly has been appointed assistant professor of pediatrics in the Department of Psychiatry at the University of Iowa College of Medicine.

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The National Foundation for Infantile Paralysis is offering postgraduate fellowships for research, and in public health and physical medicine, for physicians who wish to enter these special fields. The research fellowships are available in pediatrics, virology, orthopedic surgery, epidemiology, and neurology. Physicians who have served a minimum of two years' training on the residency level in the specialized field are eligible. Candidates must present an appropriate program of study and investigation. From a financial standpoint, awards are based on the individual qualifications and need of each applicant, and will include a monthly allowance, laboratory and other expenses deemed advisable for carrying out the program. Selection of candidates will be made by committees composed of qualified scientists. Detailed information may be obtained from the Foundation, 120 Broadway, New York 5, N. Y.

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The Maurice Lamm Blatt Memorial Fund wishes to announce a prize of \$250.00 to be given for a piece of original research work done by an Intern or Resident of the Cook County Hospital or a former Intern or Resident who has been out of the Hospital for a period of not more than five years. All communications should be addressed to the Maurice Lamm Blatt Memorial Fund, Children's Division, Cook County Hospital.

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Dr. Stanley Gibson is retiring on Jan. 1, 1949, as Chief of Staff of the Children's Memorial Hospital in Chicago, having attained the normal retirement age during the current year, but will continue on the medical staff as consulting cardiologist. Dr. John A. Bigler has been appointed Chief of Staff of the Hospital, effective Jan. 1, 1949.

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At the annual meeting of the National Committee for Mental Hygiene in November, the Lasker Award in mental health was given to Dr. C. A. Aldrich of Rochester, Minn., for outstanding accomplishments in the education of physicians in the psychological aspects of the practice of medicine.

## Book Reviews

**Pediatric Nursing.** Gladys S. Benz, R.N., M.A., St. Louis, 1948, The C. V. Mosby Company, 638 pages. Price \$4.00.

This new text on pediatric nursing is in many respects the most satisfactory discussion of the subject that has appeared. The author has had a broad experience of nursing and instruction in children's hospitals in Minneapolis, Chicago, St. Louis, and Albany, which the text reflects. Perhaps one of the reasons we like it so much is that it is really a text on pediatric nursing and not an abridged text on pediatrics for nurses like some of the books in the field. For example, the excellently illustrated discussion of infant feeding gives in detail the preparation of the formula and the technique of the milk laboratory in the hospital, but does not go into the detail of prescribing the formula. A most unusual comprehensive bibliography is attached to each section for the nurse who for some reason or other desires to go more fully into the subject. The author has also prepared a separate "Teacher's Guide" for use by the instructor in pediatric nursing. The style is pleasant and easy reading, and the text is obviously the work of the author and not something just copied and cut down.

B. S. V.

**Malaria in Kindesalter (Malaria in Childhood).** Albert Eckstein, Basel and New York, 1946, S. Karger, 119 pages. Price Swiss frs. 15.

This book gives a rather complete survey of the prophylaxis, clinical manifestations, and therapeutics of malaria in childhood, of which the author in his present position in Ankara obtained an enormous experience within a relatively small number of years. The extensive discussion of many complications of malaria in childhood, all illustrated by a short report of clinical cases, will be highly appreciated by the reader, as will be the chapter on the mutual influence of malaria and other diseases in childhood (in the author's region especially noma). It is to be regretted that the references cited by the author are restricted with the result that some recent fundamental literature and findings on the subject are lacking.

v. C.

**1948 Year Book of Pediatrics.** Edited by Henry C. Poncher, M.D., Chicago, Year Book Publishers, Inc., 541 pages. Price \$4.50.

The annual "Year Book" of pediatrics has a new editor. There is an excellent selection of material from the pediatric literature of the world with emphasis on subjects of interest and value to the general practitioner for whom the book is primarily intended. The abstracts are clear and well written. The editor has occasionally injected comments which the reviewer feels could well be extended in subsequent volumes as it is pertinent and to the point. This year's volume is decidedly better than the last few volumes, due in part no doubt to the hospitals and clinics getting back to a normal productivity after the personnel and teaching problems of the war.

**Your Baby.** Gladys D. Shultz and Lee Forrest Hill, M.D., New York, 1948, Doubleday and Company, Inc., 278 pages. Price \$3.50.

This is the most elaborate book on infant care that has appeared. It is a large book more suited for the table than for the shelf, and the format and illustrations are most attractive. The authors are a well-known editor of women's magazines who is obviously responsible for the style of the text, collaborating with a well-known pediatrician who is and trends. The last forty pages contain elaborate records to be kept up by the mother. By experience we know they will be started and soon discontinued. In this specific case as to the child's personality, and the like, will never be started, as a grown child reading over the record would probably develop a loathing for the parent. We can prophesy a tremendous sale of the book as a "gift" to the mother with her first baby.

**Hospital Trends and Developments (1940-1946).** Edited by A. C. Bachmeyer, M.D., and Gerhard Hartman, Ph.D., New York, 1948, The Commonwealth Fund, 819 pages. Price \$5.50.

This book is an extremely useful compilation for hospital administrators, students in hospital administration, medical administrative officers, deans of medical schools, and other clinical department heads who have a definite interest in hospitals.

It is a successor to "The Hospital in Modern Society" which covered a period in hospital literature between 1930 and 1940. The present volume deals with the years 1940 to 1946. There is little change, except in Part One. This section shows a very definite and new emphasis on preventive medicine and positive health, featuring such writers as Isadore S. Falk, V. M. Hoge, M.D., and Thomas Parran, M.D., of the Public Health Service. There are comments on the community hospital and public health by Ira V. Hiscock, Professor of Public Health at Yale, discussion on rural hospital and health facilities, and the latest health developments in foreign countries.

The contents of the book are well selected and reflect the condensed thinking of the most active leaders and administrators in the field of hospital service. In this compact volume almost the entire hospital field is so covered that the reader, by checking the contents, may find it a useful and handy index. Under the chapter on "Special Services," psychiatric care is featured under the authorship of Karl Menninger, M.D., and communicable diseases are given considerable space and discussion. For some reason, which is not known, pediatrics does not receive a special chapter, but is considered in the general approach in several articles. Also, the subject which relates to both pediatrics and psychiatry—the child guidance clinic—is not featured in chapter form. All in all, the book is an excellent one for people interested in hospitals and medical administration and should be available to medical, nursing, and social service staffs. It is clear that articles are chosen for their objective presentation of problems and their solution, and the editors have selected such articles with the idea of stimulating thought, regardless of the views of the editors themselves; in fact, some articles are in disagreement with their opinions.

F. R. BRADLEY

**Therapy Through Interview.** Stanley G. Law, New York, McGraw-Hill Book Company, Inc.

An essential part of psychiatric diagnosis and therapy is the interview with the patient. Dr. Law, a general practitioner for twelve years, describes the technique of interview which he has found most useful.

He calls attention to the three phases of therapy: resistance to the therapist; acceptance of help; separation from the therapist and independence. Knowing the stages through which the patient passes will help the beginner to recognize progress in therapy. Dr. Law's technique through interview is to proceed as rapidly as is consistent with the patient's attitude. He stresses the need to have the patient work out his own problems. Dr. Law leads him, pushes him, helps him to express his feelings and to make decisions but is careful not to influence him. He accepts his patient and his aggressions from the start, and this frees him from his feelings of guilt. This done, half the battle is won.

The technique seems simple enough and, with real interest and some study, most physicians could undertake this kind of therapy although it is time-consuming for the interviews do not always go smoothly. Dr. Law stresses the importance of a mature personality in the therapist. He must be able to accept the changes which the patient desires in his personality and not build up a concept of what he wishes him to be as a result of the therapy.

The book is simply, often entertainingly, written. The language is clear, and terms, which may have doubtful meaning to the general practitioner, are avoided. The case histories and explanations are so concrete that it is easy to identify oneself with the doctor interviewing the patient.

Dr. Law clarifies a form of therapy used both unconsciously and consciously by many physicians in the handling of emotional difficulties in their patients. He presents a clear picture of the mode of approach to the problems. Best of all, because of his prompt and good results in so many cases, he will give confidence to the physician who would like to help his own patients rather than sending them elsewhere for psychiatric treatment.

RUTH BAKWIN

## Editor's Column

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### DIAGNOSIS OF CONGENITAL MALFORMATIONS OF THE HEART

AMONG those in the audience at the recent meeting of the American Academy of Pediatrics in Atlantic City who listened to the Symposium on Congenital Heart Disease by Gibson, Taussig, Bing, Keith, Blalock, and Potts, must have been many whose thoughts, spoken or unspoken, reverted back to the time only a few years ago when the best that could be done in congenital anomalies of the heart was an attempt to identify the lesion for purposes of prognosis relative to disability and life expectancy. By comparison, the methods employed today in the diagnosis and surgical management of malformations of the heart and great vessels are little short of miraculous. They represent a triumph of medical science which deserves documentation among the great advances of all time.

Three rather distinct methods have evolved for the study and recognition of congenital heart defects. Demonstration that certain abnormalities are susceptible to surgical attack has, of course, stimulated research in all three fields. Children with congenital heart disease are of common occurrence in all pediatric clinics, and the problem of weeding out the operable from the inoperable has to be met constantly. Hence, most pediatric hospitals sooner or later will have to consider the question of the method or methods of study which shall be adopted in their particular institution, even though it be for the purpose of selecting cases to be sent on to the center whose facilities include those of the cardiac surgeon.

Angiocardiography has become an established diagnostic procedure. Castellanos began his studies in this technique as early as 1936. Demonstration of its value in the cyanotic group of infants and children by intravenous injection of Diodrast is clearly set forth in an article in the November issue of THE JOURNAL OF PEDIATRICS by Carson, Burford, Scott, and Goodfriend, and in the December issue of the JOURNAL, Carson and Burford have shown the remarkable clarity with which coarctation of the aorta and patency of the ductus arteriosus can be roentgenographically visualized following retroarterial injection of Diodrast into the left common carotid artery. Although these techniques possess obvious advantages, especially in borderline or obscure cases, nevertheless it must be emphasized that they are highly technical procedures requiring a team of experts, automatized radiographic equipment, and a special, rather expensive hospital setup. Nor are they entirely devoid of danger, since an occasional death has occurred even in the hands of the most experienced. It is conceivable that eventually angiocardiography may become as safe for properly selected cases as is intravenous pyelography, and that roentgenologists and clinicians will become equally adept in technical performance and interpretation of roentgenograms. But until that time comes, if it does, it would seem

that the nationwide needs of the children with congenital heart disease might best be met by a limited number of strategically located units whose personnel includes individuals with special training and experience in this particular diagnostic approach.

Almost the same comments could be made about catheterization of the chambers of the heart as a method of diagnosis in congenital heart disease as were made about angiocardiology. It, too, is a highly technical procedure, but perhaps involves less risk to the patient.

Taussig has stressed that the majority of malformations of the heart can be accurately diagnosed by methods which do not require either catheterization or angiocardiology. In her excellent book she states that "accurate diagnosis of the nature of the malformation is usually made possible by the information derived from physical examination, x-ray, fluoroscopy, and electrocardiology." Obviously, this method has the advantages that it is completely safe for the child and that it is available to every clinician. Many children in Taussig's clinic, and in others, have had the correctness of a diagnosis arrived at by the studies enumerated above confirmed at operation. It will take time before final evaluation can be made as to the advantages of the additional information derived from catheterization or angiocardiology in the diagnosis and surgical management of congenital heart disease. There is no question but that all three methods should and will be continued. But the point of these remarks is that, perhaps, the more technical procedures are best carried on in large centers by experienced workers.

L. F. H.

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### THE EWING REPORT

In an editorial in the December issue attention was called to the importance and significance of the Ewing report on the nation's health. Dr. Richard Smith has kindly abstracted the report for the JOURNAL readers which appears on page 120 of this issue. The JOURNAL is taking no position pro or con. It is simply that we feel the report is of so much importance that its content should be known by every physician.

B. S. V.

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## Original Communications

### THE BABY'S DIAPER WITH SUGGESTIONS FOR ITS IMPROVEMENT

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CLEVELAND, OHIO

THE only consideration given by pediatricians to diapers has apparently been recognition of their weaknesses. In the scanty references to the subject, the diaper is the one item of clothing deemed essential. Yet of all mammalian young, only the human infant is diapered. From considerations of the personal health of the infant, rather than the dictates of environmental sanitation or of infant fashions, the best diaper would probably be none at all, and in some parts of the world babies do not wear diapers. But in all civilized portions environmental factors are given consideration and babies now do and probably will continue to wear diapers.

The normal young infant voids a dilute, watery urine of low specific gravity and of large volume in proportion to body weight. The times a day he voids number usually from ten to fourteen, depending somewhat on season and temperature, but much less so than in the adult. In addition, the infant has, if breast fed, three or more stools a day and, if bottle fed, one or two stools daily, usually formed, moderately firm, and not of foul odor. Some time early in the process of civilization, mothers devised the diaper to catch these excrements, perhaps the earliest practice of sanitation. In the intervening centuries, new programs of sanitation have arisen, been subjected to tests, and have been abandoned or adopted; a profession of sanitarians and sanitary engineers has developed, but one of the earliest achievements, diapering, has remained essentially unchanged. There are villages in remote parts of the world where community sanitation is nonexistent. Water is obtained from open wells. Sewers do not exist. Even outhouses are too modern. The common place for male adults to deposit their excreta is in the street in front of the house, to one side of the front door. But within these houses diaper practice is essentially the same as in our modern, most sanitary cities.

The skin of a young infant is thin, delicate, and quite susceptible to irritation, which responds poorly to treatment and is easier of prevention than of cure. The least complex reaction to wet diapers is maceration of the skin in its folds, especially observed in fat infants, and caused by moisture and friction.

From the Babies & Childrens Hospital of Cleveland.

of opposing skin surfaces, resulting in painful, reddened, weeping areas, scalded in appearance. This disorder, intertrigo, is due apparently to prolonged contact of opposing skin layers constantly moist with normal urine, or, in other parts of the body, with normal sweat. Treatment requires little except the application of warm, dry air, achieved best by keeping skin surfaces separated by nonabsorbent material and by letting the infant remain for a few days without diapers.<sup>1, 2</sup>

The next type of skin disorder is a reaction to a process occurring in the wet and soiled diaper that is not promptly changed.<sup>3, 5</sup> Urine, even if sterile when passed, is immediately contaminated by organisms on the skin from present or previous fecal discharges. Maintained near body temperature, the wet diaper becomes a breeding place for more bacteria which may produce enough ammonia from urea in the urine to cause the all too familiar diaper rash or ammoniacal dermatitis, characterized first by reddening of the whole diaper area, in male infants especially over the lower abdomen and anterior surfaces of the thighs, then by roughening of the skin into an eczematoid appearance, with finally the development of denuded, weeping, shallow ulcers. In male children, crusting of the meatus with scab formation and bleeding may produce some interference with urination. Unlike intertrigo, in diaper rash skin folds are protected from the ammoniacal irritation and remain free from the disorder. Treatment of ammoniacal dermatitis again requires little except exposure of the irritated areas to warm, dry air, achieved by omitting diapers. Recurrences may be prevented by impregnating diapers with a mild, nonirritating antiseptic that will keep down bacterial decomposition of urea into ammonia, and by changing diapers more often.

Even more serious has been the implication that wet, bacteria-laden diapers held in contact with the external urinary orifice, especially in females, may be responsible for the occurrence in this sex of ascending urinary tract infections with pyuria due to cystitis or pyelitis.<sup>6</sup> Certain it is that pyuria is much more common in female infants than in males,<sup>7</sup> occurring in the latter usually only where congenital anomalies are present in the urinary tract. It is stated further by medical observers in backward countries, that pyelitis is seldom seen in native populations where, be it coincidence or otherwise, diapering of babies is most sketchy.

Urinary tract infections occur twice as often in infants and children under 2 years of age as in any other period of childhood, an age incidence corresponding sharply with the diaper period. Among the uncomplicated cases, from 63 to 90 per cent occur in girls. This disproportionate sex incidence has usually been ascribed to diaper infection, an ascending infection, supported by observation that in the neonatal period, in late childhood, and in proved hematogenous renal infection, incidence is the same for boys and girls.<sup>8, 9</sup> Helmholz has cited a family of two boys and four girls. Each girl, during the diaper age, suffered a severe renal infection; the boys escaped. Helmholz believes most of these infections are of ascending type. Undoubtedly other factors, nutrition, state of hydration, renal anomalies, repeated infections,

and gastrointestinal disease, may predispose to the infection. Perhaps relative dehydration and resultant lessened frequency of urination may account for an increase noted in summer months. In infants of diaper age, organisms of the colon typhoid group are usually incriminated as causative agents of urinary tract infections. Though many of the recurrent and more serious conditions may have their basis in an anomaly of the urinary tract, the development and severity of infection may well be related to constant local presence of pathogenic organisms. In what other circumstances, except with a diapered baby, would we permit prolonged contact of a susceptible part of the body with the organism most commonly involved in infections of that and adjacent tissues? Yet in female infants pyuria due to the colon bacillus is among the common illnesses.

Even anomalies high in the urinary tract, such as ureteral obstruction due to aberrant vessels, may lead to ascending infections. Helmholtz has shown in animal experiments that infection may ascend urogenously without obstruction in the lower urinary tract.<sup>10</sup> Perhaps it is effectiveness of direction of flow that ordinarily prevents ascending infection, since fecal infection of the urethra is ever present in infants of diaper age.

While it is apparent that several authors have recognized the menace of the diaper in the etiology of pyuria and have advised a scrupulous cleanliness of the external genitalia, especially in female infants, as the best prophylaxis against urinary tract infection, there is little evidence that consideration has been given to altering diaper practice.

The foregoing represents only part of the problem, the part relating to the local disorders in the infant traceable to wet or soiled diapers. Is there a public health problem? A study from 1936 to 1940 of hospital infections and modes of spread of infection in infants' wards led to the conclusion that of greatest moment was the transmission from infant to infant of respiratory, droplet, or airborne infection, and that gastrointestinal disorders were of secondary significance.<sup>11</sup> Over a period of years gastrointestinal disease of infants has been partially controlled apparently through improvement of milk supplies, widespread use of refrigeration, reduction in numbers of flies, and careful screening of wards. Recurrent outbreaks of intestinal disease in newborn infants' nurseries, and less severe but troublesome incidence in other nurseries, keeps forcing attention to possible weaknesses in technique of handling excreta. Here, improvement has been minimal. Urine of a healthy infant might scald his skin, but it presents little danger to the neighboring child. Stool-contaminated fingers of the nurse or attendants were probably the usual means of transfer of enteric disease. Stool soaked in urine and spread throughout a diaper, over much of the baby, and out onto the bed, would be especially difficult to confine. In what other activity are food handlers allowed alternately to handle excreta as do the mother and nurse who, immediately prior to putting a nipple on a baby's bottle, change his bed or change his diaper? Clearly these functions of the attendant should be separated by a careful washing of the hands, or, better still, through performance by different persons. Much care and cleanliness in a food formula laboratory may be lost at the infant's bedside. However,



even if all nipples are placed on bottles in food laboratories, danger of spreading enteric disease is not completely avoided, because with current diaper practice it is impossible to prevent contamination of the bed and of the whole baby in a soiled bed.

Viewed as a problem in hygiene, the diaper should serve to collect the urinary and fecal excretions in a manner not deleterious to the health of the infant and, more particularly, in a manner not conducive to the development in the infant of intertrigo, ammoniacal dermatitis, or of skin or urinary tract infections. Viewed in the light of a problem in sanitation, the diaper should serve to collect urine and stools in a manner that will limit their spread, reduce contamination of the environment of the infant, and thereby minimize danger of transmission of disease to other persons. To achieve the desired effect in sanitation, rubber pants over diapers are partially effective in that spread of feces and urine is limited. However, this result is attained only by aggravation of the hygienic problem, since with rubber pants the likelihood of all the undesirable effects of wet diapers on the baby is increased. Intertrigo is more common, dermatitis is more severe, and the chance of infection is enhanced.

Although the diaper presents an hygienic aspect and a sanitation problem, lastly, but not least, it is a garment to be applied to the infant by the mother and it must be convenient.

While ideally the diaper should be changed immediately each time it is wet or soiled, the mother can seldom do this in practice. As a garment it should not require constant changing; rather, if possible, it should require infrequent changing with minimal nursing care, to permit the infant to sleep throughout the night without irritability and wakefulness due to discomfort. It should eliminate objectionable odors in the nursery and should not increase, but should decrease laundry costs for sheets, diapers, pads, and other clothing.

Currently available diapers, either cloth or disposable, fail largely to satisfy any of the foregoing requirements.

To be hygienically sound the diaper should hold excrements away from the body; thus intertrigo and infection would be avoided. Also, the diaper should be impregnated with a mild antiseptic to prevent ammonia formation within it; thus, the incidence and severity of dermatitis would be reduced.

To be sanitarily adequate the diaper should be pocketed away from the infant effectively to catch and retain, and prevent the spread throughout the bed of urine and feces. Current modes of application of diapers, whether triangular, oblong, or panel fold, result in convexity of the diaper surface toward the infant as a roof, tending to force the stool to spread downward along the thighs and even channeling urine away from the absorptive material. These defects are even more marked in currently available disposable diapers than in the usual cotton ones. And the requirements of a garment as regards convenience, lack of expense, ease, and effective duration of application, are far from satisfactory.

An adequate diaper should meet the following requirements:

1. It should, in so far as possible, keep excretions away from contact with the infant.

2. It should minimize bacterial growth in excreted urine.
3. It should have absorptive capacity sufficient to allow the baby to remain undisturbed overnight.
4. It must be comfortable.
5. It must be convenient to change.
6. It must not be irritating either by reason of its construction or because of any of the materials in it.
7. The absorptive material should be disposable.
8. The container, or other nondisposable portion, if one is used, should be durable and easily laundered.
9. It must not be unattractive as a garment.
10. It must not interfere with changes in clothing for the infant for warm and cold weather.
11. It must compete in expense with current diapering practice.

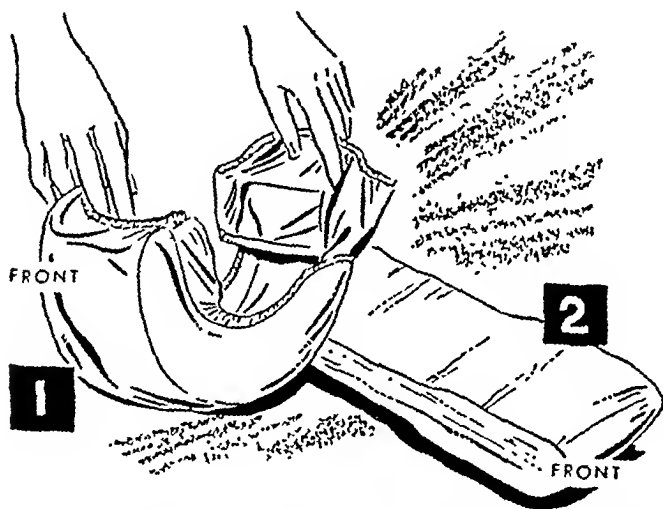


Fig. 1.—A diaper envelope (1) is constructed to hold a pad (2) which is extra thick in the front end. When properly inserted, the pad fits smoothly into the waterproof material covering both ends of the pad, keeping them out of contact with the baby, leaving only a small section in the middle of the pad directly exposed to the excretions. The arc action of the pad holds this section of the pad away from the baby. The insert can be removed by grasping the ends of the diaper garment and applying pressure in the middle with the thumbs. The folded pad will fall out.

With definition of the problem came attempts at solution.

Observation of infants in the act of voiding soon disclosed that both male and female infants void upward, the exception being the female infant with legs crossed or held tightly together, in which case some urine escapes backward. Consequently, it might be possible to collect urine anteriorly and stool posteriorly with minimal mixing. Furthermore, the external genitalia of infants grow slowly in the first year, and are at one year little larger than at birth, in sharp contrast to rates of growth of other parts of the body. Perhaps a collecting device could be designed to fit infants of any age, except the smallest premature infants.

The problem then was to make a container outside of any ordinary diaper that would collect urine and retain it away from contact with the infant's body. The first attempts resulted in the construction of rubber cuplike devices covering the genital areas and collecting urine only. Over this was worn a regular diaper, or a perforated diaper through which the cup could protrude. The collecting cup could be packed lightly with an absorbent, disposable material. Apposition to the body was obtained by flanges on the receptacle with the shape essentially of a boxer's protective cup. While this design resulted in a product useful in collecting urine specimens, it was inadequate for the intended



FIGS 2 and 3—A nylon waterproofed-lined container holds disposable pad in a form about the baby. The one tends to keep the pad out of contact with the infant. In addition, both anteriorly and posteriorly the pad holder is pocketed so that the actual opening of the collecting area toward the infant is minimal. The pad is also pocketed and of double thickness in the front to absorb the sudden expulsion of urine. The pad comes high on the abdomen, extends only a little over the buttocks in back. No discomfort from these pads has been observed in infants lying either on face or back.

purpose in that it was only 50 to 60 per cent effective and did not prevent the overlying diaper and the bedclothes from becoming wet. The principle, however, seemed sound, and tests were started with a specially designed diaper with an oblong hole in the center encompassing the genital and rectal areas, opening into an absorbent-filled, waterproof envelope secured to the outside of the diaper.

The rubber bag for collecting urine only was deemed infeasible for home use because of the difficulty in changing, skill required to fit properly to the infant, its unusual appearance with probable unacceptability for cosmetic reasons, and finally that it seemed mildly uncomfortable to the baby. The larger diaper device showed promise with first models having a high percentage of success. Further experiments were undertaken to determine details of design



Fig. 4.

Fig. 4.—Side view of experimental transparent diaper



Fig. 5.

Fig. 5.—A cast previously requiring change at frequent intervals because of soiling can be worn for long periods protected from the action of excreta by the diaper as shown above.

to insure snug fit, proportions of bag, including size of opening toward body, type of absorbent to be used, and water-tightness of the envelope. It would seem needless in a report of this sort to enumerate the steps taken to make the diaper effective and comfortable. Success ratio rose with improvements of design, and acceptability as a garment was satisfactory in tests in private homes

and institutions. Diaper rash was eliminated by use of the improved diaper. Babies slept longer and more soundly than with conventional diapers, and, most important, the purpose for which it was designed was served—urine and stool were collected effectively and were held largely out of contact with the body. While it cannot be said that simple pyuria in female infants will be eliminated through the use of such a diaper, the development represents a step toward solution of this problem at its source. No diaper odor was detectable, even in nurseries populated by eight to twelve infants. Emptying the soiled diaper could be achieved by turning it inside out with minimum contamination of the mother's hands. As a sanitary device it was not perfect, but appeared to present a large advantage over currently available models. Bed linen was seldom soiled and nursery laundry was reduced materially.

Accompanying photographs depict more clearly than descriptive details the construction, fit, and mechanism of the diaper.

#### SUMMARY

Appraisal of diapering practices leads to the conclusion that the infant's diaper presents an hygienic and a sanitation aspect as well as being the indispensable garment. Attempts have been made with considerable success to improve the diaper so that it will be hygienically adequate, sanitarily effective, and acceptable as a garment. A diaper designed to collect urine and stool of the infant with minimum contamination of the baby's body and of his bed and clothing has in clinical trials proved 95 per cent effective for these purposes, at the same time reducing incidence of intertrigo and diaper rash, and not being uncomfortable or unsightly. Whether it will reduce materially simple pyuria, a purpose for which it was designed, can be proved only by more extensive trials.

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## STREPTOMYCIN IN THE TREATMENT OF HEMOPHILUS INFLUENZAE LARYNGOTRACHEOBRONCHITIS

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THERE have been several reports of laryngotracheobronchitis due to *Hemophilus influenzae*.<sup>1, 2</sup> Rabe<sup>3</sup> in 1947 reported the bacteriologic studies on 347 cases of infectious croup in New Haven. Twenty-eight cases were due to *H. influenzae*, type B. There were fourteen cases of laryngitis (mortality 7 per cent), eight cases of laryngotracheitis (mortality 12 per cent), and five cases of laryngotracheobronchitis (mortality 40 per cent). His patients had been treated with sulfadiazine and type-specific serum. Although he reported no patients treated with streptomycin, he stated that this drug was of definite value.

Zantiny and Carlson<sup>4</sup> reported fourteen cases of respiratory infections due to *H. influenzae* treated with streptomycin. Good results were obtained in thirteen cases.

Early in January we saw three children between the ages of 6 months and one year with moderately severe laryngotracheitis due to *H. influenzae*. They were seen very early and started immediately on streptomycin. They were much improved in twelve hours and able to be sent home in four days.

Late in January we saw the first of the four infants whose cases are to be reported in detail. They were desperately ill with marked respiratory distress. The throat findings were not uniform. There was moderate retraction above the jugular notch and marked sternal retraction. The inspiratory breath sounds were rasping and there was an expiratory wheeze. There were many fine râles in both lung fields. *H. influenzae* was recovered from the throats of all four patients.

In every case there was definite improvement after twelve hours of streptomycin therapy and in seventy-two hours the patients were breathing easily.

CASE 1.—O. R. S., a 9 week old white infant, was admitted to the hospital Jan. 27, 1948, with a chief complaint of difficulty in breathing. The past history was normal except that the infant had been delivered two months prematurely. Progress until the present illness had been good, the infant weighing 9 pounds on admission.

The present illness began approximately four days before admission when he developed an upper respiratory infection with rhinitis, nonproductive cough, anorexia, and low-grade fever. Two days prior to admission the infant developed rapid breathing. These symptoms progressed rapidly until the infant was limp, cyanotic, and gasping for breath.

Physical examinations on admission revealed a prostrated infant with acute expiratory dyspnea. Respirations were elevated to 80 per minute and were gasping in character with marked sternal and intercostal retraction. The color was ashen and there was a choking cough with considerable mucus in the pharynx. On auscultation of the chest, there were squeaks and many moist râles heard throughout both lung fields. Temperature on admission

was 100.5° F. (R), and white blood cell count was 6,300 with 70 per cent polymorphonuclears (6 stab forms). A throat culture was taken. X-ray of the chest was not remarkable.

Treatment as first instituted consisted of continuous oxygen, penicillin 15,000 units intramuscularly every three hours, and a vapor tent. Within a few hours streptomycin was started with 50 mg. intramuscularly every three hours.

The temperature continued to rise for one and one-half days after admission, reaching 106° F. (R) before suddenly abating. However, the respiratory symptoms improved markedly within twelve hours. The throat culture taken on admission grew a pure culture of *H. influenzae*. Repeated throat cultures three days after admission were negative for *H. influenzae*. Repeated blood counts reached a height of 11,600 white blood cells, with 44 per cent neutrophils and 56 per cent lymphocytes. Respirations returned to normal three days after admission. Streptomycin was discontinued on the fourth hospital day, and penicillin on the sixth day.

CASE 2.—A. F., a 6-month-old female infant, was admitted to the hospital Feb. 3, 1948. Chief complaint was cough and choking respirations. Past history revealed normal growth and development complicated for several months by a chronic cough. In January, x-rays of the chest, including barium swallow, were normal. Two months prior to present admission the infant had early bronchopneumonia treated in the hospital for a short time with penicillin. Recovery was uneventful.

The present illness began approximately a week before admission when the infant developed a "croupy" cough associated with rhinitis, and was treated on an out-patient status with vaporizer and aspirin. She ran a low-grade fever and developed progressive respiratory difficulty and increasing cough. She was able to take but small amounts of formula. The infant was not dangerously ill on admission but had rapid, gasping respirations without cyanosis.

Positive findings on physical examination were limited to the pharynx and chest. The former was moderately inflamed. The respiratory rate was increased and dyspnea was present. Auscultation of the chest revealed expiratory wheezing and moist rhonchi throughout both lung fields. There was a grade III, systolic, machinery murmur heard in the pulmonic area. Initial blood count showed 16,750 white blood cells with 30 per cent neutrophils and 70 per cent lymphocytes. X-rays of the chest were normal. A throat culture was obtained.

Treatment on admission consisted of vaporizer, continuous oxygen, and penicillin 15,000 units intramuscularly every three hours. The temperature was 100.3° F. rectally on admission and climbed steadily. The throat culture was reported to grow *H. influenzae* on the second hospital day, and streptomycin 50 mg. intramuscularly every three hours was started. The temperature continued to rise until about twelve hours after streptomycin was instituted, when it reached 105.8 F. rectally and then fell rapidly by crisis. The clinical symptoms improved rapidly with reduction in respiratory rate and coughing. The temperature fell to 101° F. rectally on the third hospital day and was normal at the end of the fourth day. A throat culture on the fifth hospital day was negative for *H. influenzae*. Streptomycin was discontinued on the fifth and penicillin on the sixth hospital days and the patient was discharged.

CASE 3.—W. P., a 4-month-old Negro male infant, was admitted to the hospital on March 2, 1948, with a chief complaint of difficulty in breathing and fever. Family and past history were noncontributory.

Four days before admission the infant developed typical coryza. On the day of admission fever and acute dyspnea developed. This was treated with aspirin and vaporizer, but responded poorly. There was a large amount of mucus discharge and the infant was unable to take fluids well.

The pharynx was injected and the nasopharynx was congested with large amounts of mucus discharge. There was severe dyspnea with sternal and intercostal retraction. On auscultation of the chest moist, inspiratory râles were heard all over both lung fields and there was some dullness and diminution of breath sounds over the right middle chest posteriorly.

Admission temperature was 102° F. rectally and the white blood cell count was 22,300, with 64 per cent neutrophiles. A throat culture was obtained and a chest x ray showed partial collapse of the right upper lobe with shift of the mediastinum to the right.

Treatment was first instituted consisted of penicillin 15,000 units intramuscularly every three hours, oxygen, suction when needed, and a steam tent. Eighteen hours later when the first throat culture was reported to be a pure culture of *H. influenzae*, the patient's condition was worse. The infant was suctioned and turned frequently, and streptomycin was started, 100 mg intramuscularly every three hours.

The clinical course improved markedly after streptomycin was instituted. The temperature fell nearly to normal and the respirations, which had been up to 80, gradually decreased. Daily throat cultures were obtained and failed to grow *H. influenzae* a day and one half after streptomycin had been instituted. Three days later the respirations and temperature were back to normal, and x ray of the chest demonstrated re expansion of the collapsed lobe, and a normal chest. The streptomycin was discontinued three days after its institution. The white blood cell count at this time was 10,700 with 44 per cent neutrophiles. The infant was discharged from the hospital on the eighth hospital day.

In this case an in vitro sensitivity test was run to determine the sensitivity of this particular strain of *H. influenzae* to various dilutions of streptomycin. The paper disc method was used. The discs were moistened with various dilutions of the streptomycin and placed on a plate evenly seeded with the *H. influenzae* cultured from the patient. The result demonstrated that this particular strain was sensitive to dilutions as low as 0.1 unit per cubic centimeter.

CASE 4—M. N., a 4 month old female infant, was admitted to the hospital on March 5, 1948, with a chief complaint of fever and respiratory distress. Family and past history were noncontributory.

Present illness began with an upper respiratory infection about a week before admission. On the night of admission she developed rapid, wheezing respirations, cyanosis, and fever.

Physical examination revealed dyspnea with respirations of 64 to 80 per minute and moderate intercostal retraction. There were moist inspiratory rales throughout both lung fields. The pharynx was inflamed. Temperature was elevated to 102° F rectally. The white blood cell count was 15,550 with 64 per cent neutrophiles. A throat culture was taken. X ray of the chest showed clouding of the right upper lung field and a diagnosis of early pneumonia was suggested.

Treatment at first consisted of penicillin 20,000 units intramuscularly every three hours, and vaporizer. The initial throat culture grew out only *Staphylococcus aureus*. The infant seemed to improve during the first two days, but on the third hospital day the temperature rose again to 103° F rectally and breathing seemed more labored. The pharynx was still markedly inflamed. A throat smear at this time revealed predominant gram negative bacilli, suggestive of *H. influenzae*, and streptomycin, 100 mg every three hours, was started. This was on the third day of hospitalization. The throat culture at that time grew out predominantly *H. influenzae*. Apparently the infection was initially a mixed one, and the penicillin therapy eliminated some of the pathogens, allowing the *H. influenzae* to overgrow the others.

Improvement was steady following the administration of streptomycin. The temperature fell to normal the next day, the fourth hospital day, and the respirations returned to normal. Repeated throat culture was negative for *H. influenzae* the day after streptomycin was started. X ray of the chest on the fifth hospital day showed normal lung fields and the white blood cell count was 7,700 with 15 per cent neutrophiles. The infant was discharged from the hospital on the tenth hospital day.

#### DISCUSSION

It will be apparent that it is not possible to determine the infecting organism in cases of tracheobronchitis in young infants by clinical methods or from



the blood picture. Rabe<sup>3</sup> observed that most of the New Haven patients with *H. influenzae* tracheobronchitis had a cherry red epiglottis. This was not present in any of our cases. It is probable that the clinical picture in the younger age group is different from that seen in older infants. The bronchial symptoms predominate in the young infant.

Because of the excellent response to streptomycin in the reported cases and the high mortality in this disease, we are now starting streptomycin on all cases in real distress from tracheobronchitis on admission and continuing the drug until the throat culture is reported. Unless the culture reveals a streptomycin-susceptible organism, the drug is discontinued. We have treated a number of cases in this manner, and none have shown any ill effects from the streptomycin. A review of the literature reveals no reports of serious ill effects from streptomycin given such a short period of time. The culture from two cases of bronchiolitis treated with the regimen showed *B. friedländer*. Both infants responded rapidly.

No clinically resistant strains of *H. influenzae* were encountered. Alexander and Leidy<sup>5</sup> found a small proportion of resistant members in each of ten strains from cases of meningitis they studied. They felt that resistant members of the strain were of clinical importance only when the initial bacterial population was very large. The resistant cases reported by Harris and collaborators<sup>6</sup> had been ill for some time before therapy was instituted and were probably infected by a large number of organisms. Laryngotracheobronchitis in infants is a very acute disease and those that succumb do so quickly because of the smallness of the infant's tracheo and bronchial tree. It is possible, therefore, that the bacterial population is not so large that resistance will be met too frequently in this disease. It is not possible to draw any conclusions from the small number of cases seen by us.

#### CONCLUSION

1. Four cases of *H. influenzae* laryngotracheobronchitis in young infants successfully treated with streptomycin are reported.
2. The lack of clinical characteristics in young infants that would identify the etiology of the disease is shown.
3. It is suggested that streptomycin be given immediately to all cases of laryngotracheobronchitis occurring in young infants and continued until the throat culture reveals a nonsusceptible organism.

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## PRIMARY OVARIAN AGENESIS

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ALTHOUGH noted by Olivet<sup>1</sup> as early as 1923, the association of shortness of stature and sexual infantilism, consisting of failure of development of secondary sex characteristics and primary amenorrhea, was first described in this country by Turner<sup>2</sup> in 1938. The latter reported seven cases in girls or young women in whom there was also present since birth webbing of the neck and an increase in the carrying angle at the elbows (*enbitus valgus*). He ascribed the shortness, the moderately retarded osseous development, and the sexual retardation of his patients to a pituitary deficiency. Unfortunately, no hormone assays were performed on these patients, so that the exact nature of the deficiency was not determined. However, the close correspondence between the symptoms of Turner's patients and those of patients described by others indicate that these young women were suffering from an ovarian deficiency rather than from pituitary disease. In 1942, Varney, Kenyon, and Koch<sup>3</sup> described four young women of short stature, moderately retarded osseous development, very much retarded breast development and genital development, and either amenorrhea or infrequent menses, although they exhibited the growth of a small amount of pubic and axillary hair. In two of their patients who were studied, very low quantities of urinary estrogens were found, while urinary androgens were only moderately reduced. They demonstrated that these symptoms were due to an ovarian deficiency rather than to a deficiency of the pituitary, or to a deficiency of both glands. In their discussion of the seven autopsy reports on similar cases in the literature, they emphasized that in all these cases no normal ovarian tissue had been found, while the pituitary had been intact.

A complete description of this syndrome was presented by Albright, Smith, and Fraser,<sup>4</sup> who reported eleven patients. They pointed out that although lack of sexual development associated with decrease in stature usually brings to mind panhypopituitarism, the deficiency from which these patients were suffering was primary in the ovary and presented the following features:

1. Shortness of stature, but not the dwarfism which is found in panhypopituitarism.
2. The presence of axillary and pubic hair, although decreased in amount. This is never found in panhypopituitarism.
3. Infantile breasts, uterus, vagina, and labia, not unlike that found in hypopituitary disease.
4. The patients are strong, well nourished, and unlike the frail, easily tired pituitary dwarf.
5. Moderate retardation of skeletal maturation. Epiphyseal closure is delayed but occurs eventually. In hypopituitary dwarfs epiphyseal union is often delayed indefinitely.

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the blood picture. Rabe<sup>3</sup> observed that most of the New Haven patients with *H. influenzae* tracheobronchitis had a cherry red epiglottis. This was not present in any of our cases. It is probable that the clinical picture in the younger age group is different from that seen in older infants. The bronchial symptoms predominate in the young infant.

Because of the excellent response to streptomycin in the reported cases and the high mortality in this disease, we are now starting streptomycin on all cases in real distress from tracheobronchitis on admission and continuing the drug until the throat culture is reported. Unless the culture reveals a streptomycin-susceptible organism, the drug is discontinued. We have treated a number of cases in this manner, and none have shown any ill effects from the streptomycin. A review of the literature reveals no reports of serious ill effects from streptomycin given such a short period of time. The culture from two cases of bronchiolitis treated with the regimen showed *B. friedländer*. Both infants responded rapidly.

No clinically resistant strains of *H. influenzae* were encountered. Alexander and Leidy<sup>5</sup> found a small proportion of resistant members in each of ten strains from cases of meningitis they studied. They felt that resistant members of the strain were of clinical importance only when the initial bacterial population was very large. The resistant cases reported by Harris and collaborators<sup>6</sup> had been ill for some time before therapy was instituted and were probably infected by a large number of organisms. Laryngotracheobronchitis in infants is a very acute disease and those that succumb do so quickly because of the smallness of the infant's tracheo and bronchial tree. It is possible, therefore, that the bacterial population is not so large that resistance will be met too frequently in this disease. It is not possible to draw any conclusions from the small number of cases seen by us.

#### CONCLUSION

1. Four cases of *H. influenzae* laryngotracheobronchitis in young infants successfully treated with streptomycin are reported.
2. The lack of clinical characteristics in young infants that would identify the etiology of the disease is shown.
3. It is suggested that streptomycin be given immediately to all cases of laryngotracheobronchitis occurring in young infants and continued until the throat culture reveals a nonsusceptible organism.

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in her hip. The pain was present even at rest but was aggravated by motion. She developed low-grade fever and although she ate fairly well, began to lose weight. Every few months for the next three years there developed a stiffness and intermittent pain in the left hip, radiating to the left buttock, groin, and upper anterior surface of the thigh and lasting for several weeks. There was usually low-grade fever and occasionally swelling of the left knee and ankle, and once of the right knee. Between attacks she felt fairly well and went to school.

After three years of these attacks, a plaster body spica was applied, including both legs. This was kept on for six weeks. There resulted considerable improvement in her symptoms for about a year and one-half, and she began to gain weight again. About six months prior to admission the pain recurred, as severe as it had been previously, and she again required prolonged bed rest.



Fig. 1.—Patient on admission before therapy. Ovarian agenesis.

Her parents were each 53 years old. Her mother was short, of about the same height as the patient. There was one other sibling, a girl three years her junior, who was in good health and of normal height. The patient had always been short for her age. Although 16 years old, she had never menstruated.

Upon examination, the patient appeared to be small, thin, poorly developed, and undernourished. She was nervous and apprehensive and her emotional, intellectual, and

6. Increase in FSH (follicle stimulating hormone of the pituitary), whereas in hypopituitary dwarfs FSH is absent.

7. Presence of 17-ketosteroids in the urine, although moderately reduced in amount; the urine of hypopituitary dwarfs usually contains very little 17-ketosteroids.

8. Estrogenic therapy produces an increase in sexual hair in these patients, but not in hypopituitary dwarfs.

9. Carbohydrate metabolism, as indicated by the reaction to hypoglycemia (insulin tolerance test) and by the reaction to hyperglycemia (glucose tolerance test) is normal in these patients but not in hypopituitary dwarfs.

10. Diffuse osteoporosis, which is an expression of estrogen lack in these patients.

11. The frequent presence of other congenital anomalies, such as webbing of the neck, coarctation of the aorta, ocular changes, etc.

Albright and his co-workers maintained that the development of pubic and axillary hair is a function of the adrenal cortex rather than of the ovary, a point of view which is shared by most observers. Hence, the presence of sexual hair in a patient with obvious estrogen deficiency is an indication that the adrenotrophic function of the pituitary gland is intact, and is suggestive evidence that the estrogen lack is not caused by panhypopituitarism. They were convinced that the primary disturbance in these patients was an ovarian deficiency because of the similarity of their cases with those described in the German literature, in which autopsy findings had revealed either the complete absence of ovaries, or their presence in an embryonal state. A report of six more cases by Schneider and McCullagh<sup>5</sup> described clinical features identical with those already indicated in previous reports. The latter authors felt that the shortness in stature is probably a congenital characteristic. In 1944 Wilkins and Fleischmann<sup>6</sup> offered a complete description of this syndrome, presenting in detail the clinical features, and reporting three more cases in which biopsy studies showed a total lack of ovarian development, thus demonstrating without any doubt that the cause of the symptoms was a primary deficiency of the ovary. They, too, were of the opinion that the delayed growth in height was of genetic rather than of endocrine origin.

The signs and symptoms of the syndrome are fairly clear-cut and the condition should be easily recognized. Some variations in its features have been described and as new cases are reported other variations will undoubtedly come to light. We have recently encountered a patient suffering from this condition, whose characteristics, although typical of the syndrome of primary ovarian agenesis, were at first masked by the intensity of the other symptoms for which she was admitted to the hospital.

#### CASE REPORT

R. F., a 16-year-old white girl, was admitted to the hospital for the first time on Feb. 18, 1946, with the complaint of pain in the left hip and inability to walk. She had been in perfect health up to the age of 11 years, when she began to limp because of pain

metacarpals and the epiphyses of the phalanges were as yet unfused. The distal radial and ulnar epiphyses were also not fused. At the elbow the epiphyses of the medial and lateral epicondyles of the humerus were partly open, while the epiphysis of the radial head had fused to the shaft. At the knee, the distal epiphysis of the femur and proximal epiphyses of the tibia and fibula were not fused. At the hip the epiphyses at the head and greater tuberosity of the femur were still open.

X-ray studies revealed a reticular appearance of most of the bony skeleton due to osteoporosis. This was especially marked in the pelvis and upper portion of the femora (Fig. 2), in the left tibia and patella (Fig. 3), in the vertebrae (Fig. 4), and in the tarsal bones. There was an area of rarefaction about 1.5 cm. long at the junction of the lower and middle third of the right tibia. The left hip showed marked narrowing of the joint space and flattening of the inferior mesial aspect of the femoral head. In both sacroiliac joints there were evidences of advanced arthritic changes of a destructive as well as of a productive type. There was considerable irregularity in both sacroiliac synchondroses with productive changes extending well into the ilia on both sides. Mediastinal and cardiac shadows were normal. The ribs were normal except for marked osteoporosis. There was no evidence of notching of the ribs. X-ray of the skull was negative. The electrocardiographic tracing was normal.



Fig. 3.—Osteoporosis of left tibia.



Fig. 4.—Osteoporosis of vertebrae.

*Laboratory Data.*—The sedimentation rate was 57 mm. per hour on admission and ranged between 34 and 95 mm. on repeated examinations. The blood culture was sterile. Urine smears and culture were negative. Rectal cultures were repeatedly negative for organisms of the typhoid-paratyphoid-Salmonella dysentery group. Blood agglutination against typhoid and paratyphoid was negative, but was positive twice against Salmonella in dilu-

physical development appeared to be that of a 10-year-old, rather than that of a 16-year-old girl. Fig. 1 is a photograph of the patient taken at this time. Her temperature was 100.5° F., pulse 144, respirations 30, blood pressure was 140 systolic and 90 diastolic. She weighed only 59 pounds and her height was 58 inches. Her skin was normal, except for some dryness of the upper extremities and around the abdomen and knees. There was a slight exophthalmos but the eyes were otherwise normal and reacted well to light and accommodation. The fundi were normal. Her teeth were normal and dentition was normal for her age. The ears, nose, mouth, and throat were normal. Her heart was not enlarged, the point of maximal impulse was in the fifth intercostal space in the left midclavicular line. There was no thrill. There was a blowing, systolic murmur over the pulmonic area, not transmitted. The heart sounds were of good quality. There was no evidence of pulmonary pathology and the abdomen was negative to examination. The left hip was not particularly tender to palpation but either active or passive motion caused acute pain, so that she was unable to sit up but lay flat on her back, keeping the hip flexed at a 15-degree angle. She was, of course, unable to walk. Locally, there was no heat, redness, or swelling at the joint and no evidence of fluid. The other extremities were normal at the time.



Fig. 2.—X-ray of pelvis. Osteoporosis especially marked in pelvis and upper femora. Arthritic changes in left hip.

Her body appeared rather boyish, her hips were narrow, her chest was flat, and there was no trace of breast tissue (Fig. 1). The areolae were nonpigmented and the nipples were prepubertal. There was some scant axillary hair and a moderate amount of pubic and labial hair. The labia majora and minora were infantile, and the vaginal mucosa was smooth. Rectal examination revealed a markedly hypoplastic uterus and cervix, the size being approximately  $\frac{3}{4}$  inch from external os to fundus and the cervix width was only  $\frac{1}{4}$  inch.

Neurologic examination was negative but psychometric appraisal of the patient indicated a "dull, below normal child," with an I.Q. of 80 (Revised Stanford-Binet). Her osseous development was that of a 12 to 13-year-old girl. The distal epiphyses of the

tions of 1:160 and once in a dilution of 1:80. Heterophile agglutination was very weakly positive (1:32) and the antistreptolysin titer was negative. Repeated blood counts were essentially normal, except at times for a moderate secondary anemia. Blood and bone marrow studies showed no evidence of a blood dyscrasia. Examination of the urine repeatedly revealed normal findings, and a specific gravity which varied between 1.000 and 1.024. A test for Bence-Jones protein was negative. The Kline test was negative. The intracutaneous tuberculin test was negative to 5.0 mg. Vitamin A curves were normal. The vitamin C level was 1.89 mg. per cent. The blood calcium level was about 10.0 mg. per cent on repeated examinations. The blood phosphorus was 4.9 mg. per cent and the phosphatase varied between 1.6 and 5.3 Bodansky units. The total blood protein was 7.78 mg. per cent. The fasting blood sugar was 78 mg. per cent. The blood urea was 16.1 mg. per cent. Calcium and phosphorus metabolism studies were performed but shed no light on the nature of the condition. A basal metabolic rate was minus 15 per cent. A study of the blood lipid partition revealed the following normal values: total lipids 457 mg. per cent, total cholesterol 144 mg. per cent, free cholesterol 34.4 mg. per cent, free cholesterol 23.8 per cent of the total cholesterol. The urine was negative for estrogens. The urinary output of 17-ketosteroids was 3 mg. for twenty-four hours, which is slightly below the average normal level at this age.<sup>7</sup> The urinary excretion of F.S.H. in twenty-four hours was 3 R.U. and 6.5 R.U.\* This would seem to represent a normal rather than an increased excretion of urinary gonadotropins.<sup>8</sup> However, higher values are usually obtained using the mouse unit technique. A glucose tolerance test was normal, as indicated by the following blood sugar levels after the ingestion of 175 Gm. of glucose per kilogram of body weight: fasting, 84 mg. per cent; forty-five minutes, 167 mg. per cent; one and one-fourth hours, 161 mg. per cent; two and one-fourth hours, 73 mg. per cent; three and one-fourth hours, 80 mg. per cent; four and one-fourth hours, 83 mg. per cent (Fig. 5). An insulin tolerance test also revealed normal results. After the intravenous injection of 0.1 unit of insulin per kilogram of body weight, the blood sugar levels were as follows. (Fig. 6.)

TIME	LEVEL (MG. PER CENT)
Fasting Blood Sugar	84
15 minutes	58
30 minutes	47
45 minutes	46
60 minutes	56
75 minutes	56
90 minutes	64
105 minutes	91
120 minutes	98

This indicated a normal response to the hypoglycemia induced by insulin, one which could not be obtained in the presence of hypopituitarism.

*Course.*—The patient ran a low-grade fever in the hospital. The knee and ankle joints developed swelling due to fluid which, when aspirated, proved to be of a gelatinous consistency and scant in amount. On smear, this material showed some polymorphonuclear leucocytes but no organisms, and cultures were sterile. These swellings cleared spontaneously, apparently without responding to medication. The pain in her left hip continued and, because of her position in bed, she developed a considerable amount of contracture at the left hip. A body spica was applied for two months to overcome this complication but the contracture recurred when the cast was removed. However, her pain had disappeared and there was improvement in her walk, although she continued to keep her hip flexed.

On Sept. 14, 1946, when the patient was 17 years old, she was started on hormone substitution therapy. An estrogen, di-ethyl stilbestrol was given daily in 0.5 mg. doses for twenty days followed by a ten-day rest period. Four weeks after the onset of this treat-

\*F.S.H. determinations were made in the Laboratories of the Massachusetts General Hospital through the courtesy of Dr. Nathan B. Talbot.



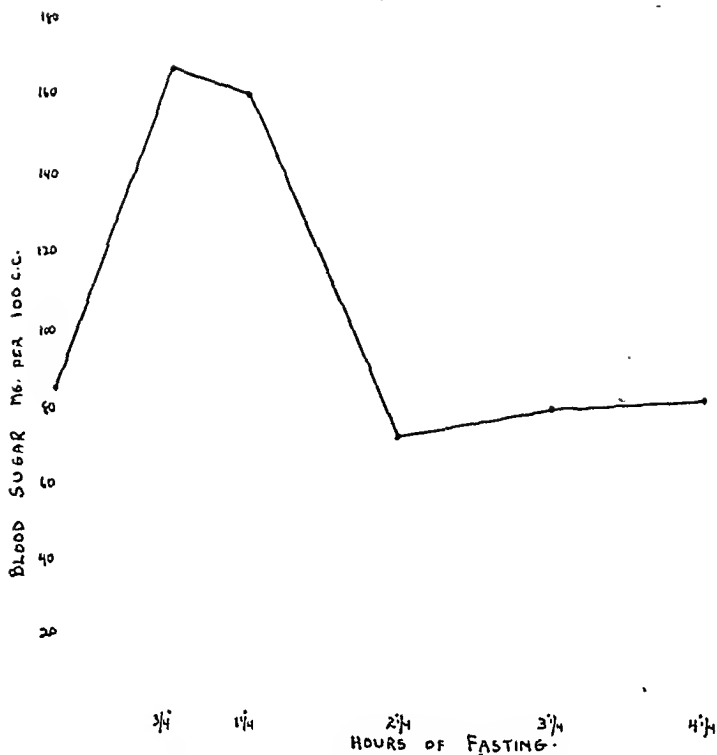


Fig. 5.—Normal glucose tolerance curve (1.75 Gm. glucose per kilogram body weight, orally).

### INSULIN TOLERANCE CURVE

(0.1 UNIT INSULIN PER KGM. BODY WEIGHT INTRAVENOUSLY)

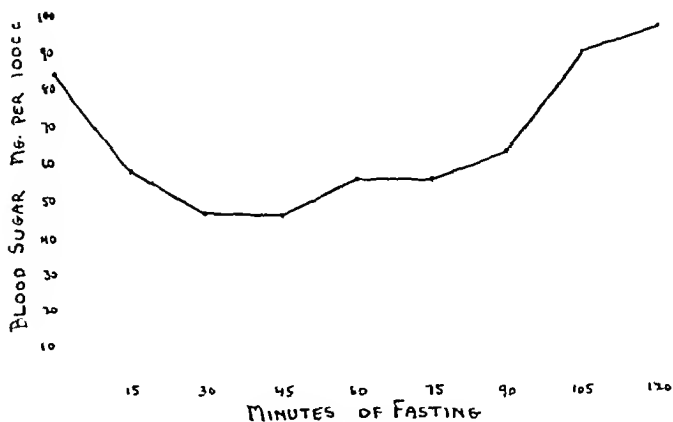


Fig. 6.—Normal insulin tolerance curve (0.1 unit insulin per kilogram body weight, intravenously).

ten days, the therapy was repeated. The patient has been maintained on this therapy to the present time. She has developed into a comely young lady of 17 years (Fig. 7). She looks well, is happy, and her psychic state during this period of adolescence is normal. Her menstruation is artificially induced and is nonovulatory, and gestation is impossible. She still has her arthritis, which is believed to be of a rheumatoid type and for which she is receiving orthopedic treatment.

#### COMMENT

The clinical picture of primary amenorrhea in a 17-year-old girl with complete absence of even the earliest signs of approaching puberty, the infantile nature of the external genitalia and of the uterus and cervix, together with shortness of stature, would of necessity make one suspect the presence of some pituitary disturbance. However, in the presence of a fair growth of sexual hair, normal excretion of 17-ketosteroids in the urine, a normal excretion of urinary gonadotropins and a normal response to the ingestion of glucose and to the intravenous administration of insulin, such a diagnosis is not tenable. The impression of a normally functioning pituitary gland in this case is further strengthened by the effect of the administration of estrogens upon the growth of sexual hair. The normal growth which occurred in this patient as a result of therapy is never found in panpituitary disease. Since the development of sexual hair is a function of the adrenals, stimulation of the adrenals by the intact pituitary is essential in order to exercise that function.

The pituitary gland exerts a profound influence upon carbohydrate metabolism, either directly or through the adrenals. Experimental and clinical investigations in that direction have been extensive and adequate and need not be discussed here. A fair picture of the degree of control of carbohydrate metabolism may be obtained by administering insulin intravenously and noting the effect of the resulting hypoglycemia and the subsequent rise in blood sugar as a result of the action of the "sugar-metabolism" or "S" hormone of the adrenal cortex. Similarly, the effect on the blood sugar curve may be studied after the oral ingestion of glucose (glucose tolerance test). In our patient both of these tests were normal, providing clear evidence that this function of the pituitary gland was also intact.

Since it appears that all of the demonstrable functions of the pituitary were operating normally, it becomes evident that the disturbance in this patient did not emanate from this gland, unless we postulate that there was a selective deficiency of its gonadotropic function, such as has been described by Albright,<sup>4</sup> and by Wilkins and Fleischmann.<sup>10</sup> Such a condition is exceedingly rare and should be accompanied by a very much reduced or absent titer of gonadotropins in the urine.

The possibility that the amenorrhea was caused by the previous prolonged illness of the patient must be considered. However, aside from the short periods during which she was confined to bed, the condition was not particularly debilitating. Although serious illness may conceivably result in delayed puberty and amenorrhea, far more severe bone disease than that suffered by this patient has been accompanied by normal menarche. The absence of the first sign of breast development in spite of the presence of fair amounts of pubic and axillary

ment there was noted for the first time a definite swelling of both breasts, the areolae became more deeply pigmented and marked vaginal leucorrhea appeared. Four weeks later the first vaginal bleeding occurred. Since then bleeding has occurred every month, after withdrawal of therapy, consisting of a fair flow lasting three to four days and quite normal in appearance. Her breasts have approached a low normal in size for her age. Axillary hair has increased and pubic and labial hair have attained almost normal growth (Figs. 7 and 8). She has gained weight (about 15 pounds in nine months) and has grown one inch, so that she is now 59 inches tall. Rectal examination at this time revealed a definite increase in size of the uterus and cervix to at least twice the previous size. There is some danger in the continuous administration of estrogen alone lest the proliferative

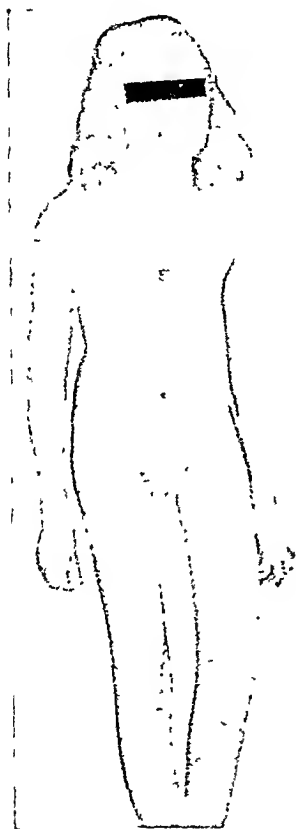


Fig. 7.

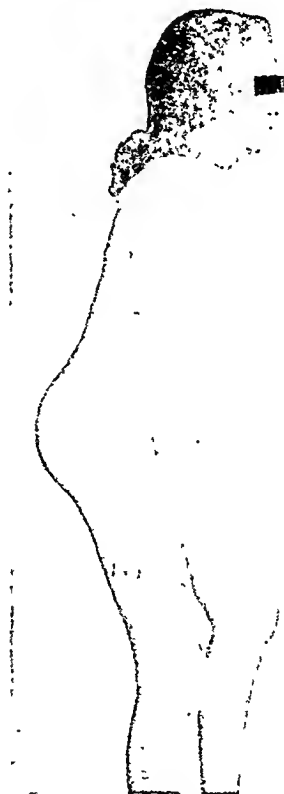


Fig. 8.

Figs. 7 and 8.—Showing patient after nine months of therapy. Breast development, abundant pubic hair, and change in general appearance.

reaction in the uterine endometrium cause excessive bleeding. The introduction of progesterone at about the time when it would appear normally in the cycle, after ovulation and corpus luteum formation, or after the second week of the cycle, causes cessation of endometrial growth. Upon withdrawal of both hormones about one week later, a more physiologic type of menstruation occurs.<sup>9</sup> Accordingly, the form of therapy was changed. Oral estrogen as Estinyl (Schering) 0.05 mg. was given once a day for twenty-one days. On the fourteenth day oral progesterone therapy as Pranone (Schering) 10 mg. was given in addition and continued daily for the last seven days. After a rest period of seven to

ten days, the therapy was repeated. The patient has been maintained on this therapy to the present time. She has developed into a comely young lady of 17 years (Fig. 7). She looks well, is happy, and her psychic state during this period of adolescence is normal. Her menstruation is artificially induced and is nonovulatory, and gestation is impossible. She still has her arthritis, which is believed to be of a rheumatoid type and for which she is receiving orthopedic treatment.

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hair, the absence of urinary estrogens and the marked osteoporosis of the skeleton, the infantile nature of the genitalia and the uterine and ovarian hypoplasia make it clear that the symptoms cannot be explained on that basis.

Skeletal development was moderately retarded to a level of about 13 years of age, in no wise resembling the marked skeletal retardation found in the hypophyseal dwarf. Evidence of fusion of some of the epiphyses to the shaft, especially about the elbow, were already present. The moderate degree of mental dullness which our patient exhibited is not at variance with that described by others. Two of the patients in Schneider and McCullagh's series<sup>5</sup> and two of Wilkins and Fleischmann's patients<sup>6</sup> showed evidence of similar retardation. Psychometric studies revealed an I.Q. of 80 by the revised Stanford Binet test, in a "dull, below normal child. Her poor memory, failure on the language completion test, and the disorganization pattern on the achievement test suggested mental aberration on an organic basis."

The patient's blood pressure was elevated on repeated determinations. This coincides with the hypertension which has been reported in these patients by others. Although elevation of blood pressure has been identified with coarctation of the aorta, in some instances of primary ovarian agenesis, there was no evidence of such an anomaly in our patient.

The cases of sexual infantilism and shortness of stature which were described by Turner<sup>2</sup> were probably instances of primary ovarian agenesis, although assays for urinary gonadotropins were not performed. In his series an increase in the carrying angle of the elbows, or cubitus valgus, was uniformly found. This characteristic has been noted only occasionally in other cases of ovarian agenesis. Our patient presented no evidence of either webbing of the neck or increase in the carrying angle. These anomalies are merely illustrations of the congenital defects which have been known to occur in this syndrome. While the type of anomaly which is seen is not consistent, the regular occurrence of some congenital deviation from the normal is noteworthy.

There was marked, generalized osteoporosis of the bones. Although preponderant in the pelvis, spine, and the long bones of the left lower extremity, the generally washed-out appearance of most of the bony skeleton was striking. Although this phenomenon is a manifestation of hypoestrinism in general and occurs after castration or at the menopause, it is, ordinarily, a characteristic feature of this syndrome. The reticulation is due to atrophy of the matrix rather than to a mineral deficiency. Whether the osteoporotic changes in the bone bore any etiologic relationship in our patient to the arthritic changes in the left hip which were of a degenerative, as well as of a proliferative nature, is problematical. In this connection, it would appear that the presenting complaint of arthritis of the left hip was purely an adventitious feature, even though it disturbed the patient far more than her sexual immaturity and almost served to obscure the underlying syndrome.

The failure of these patients to grow to a normal height such as is usually seen in hypogonadism with onset before adolescence, has been speculated upon by several writers. Because of the delay in epiphyseal closure the duration of the growth period is increased. Hence, shortness of stature should not occur if the

growth urge is normally present. The explanation most commonly advanced and the one that is the most probable is that the shortness is caused by some genetic defect, even as the other congenital defects associated with this condition. Whether or not this is so, it is evident that it cannot be accounted for by any demonstrable endocrine defect. Nevertheless, it is this shortness of stature which makes one erroneously associate the symptoms with an hypophyseal defect until it becomes evident that no such deficiency exists.

#### TREATMENT

It has already been indicated that the treatment of this condition consists entirely of substitution therapy with estrogenic substances. This brings on the sexual maturation which had hitherto failed to develop. The breasts become larger and attain normal proportions; the areola become more deeply pigmented. The labia develop and the vaginal epithelium becomes converted to the adult type. The uterus becomes larger and menstruation usually sets in. With the continued administration of estrogens, there is danger of unusual endometrial hyperplasia, with the concomitant risk of excessive bleeding. It is therefore advisable, as soon as menstruation has been established, to introduce progesterone in some form toward the latter part of the cycle. In this way, the production of a secretory type of endometrium is encouraged, and menstruation becomes more nearly normal. Our procedure has been to give estrogens alone by mouth for fourteen days and then to introduce a progestin together with the estrogens for seven more days. All therapy is then withdrawn. After hormone withdrawal, menstruation sets in shortly thereafter. After a rest period of seven to ten days, the therapy is repeated. This procedure follows the commonly accepted physiology of normal menstruation.<sup>9</sup>

It is essential that this type of therapy be avoided if the sexual immaturity is of pituitary origin, for if the ovaries are intact but are not functioning normally because of failure of pituitary gonadotrophins, ovarian atrophy may ensue. Treatment must be continued indefinitely. Gestation, however, cannot occur. The patient should be made aware of the true nature of things but should be told that marriage and marital relations are entirely possible. The psychic changes in these patients makes the tedium of indefinitely continued therapy well worth while.

#### SUMMARY

A case of primary agenesis has been described, the symptomatology and diagnosis discussed, and a plan of treatment outlined.

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## CONSTRICTING VASCULAR RINGS

### REPORT OF TWO CASES WITH RECURRENT RESPIRATORY INFECTIONS

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THE condition of double aortic arch has been described so clearly that its clinical recognition and surgical correction are becoming increasingly frequent. Symptoms are due to constriction of the esophagus and trachea by the encircling vascular ring. During infancy this anomaly most frequently gives rise to respiratory stridor.<sup>1,6</sup> Dysphagia and vomiting often appear after introduction of solid foods to the diet. Recurrent respiratory infections are also common symptoms.<sup>1,4,7</sup> Two of our recent cases have shown repeated pulmonary infections as the primary manifestation of this condition.

CASE 1.—A W was first hospitalized at 14 months of age. She appeared normal at birth and seemed well in all respects until 7 months of age when the parents first noted occasional "crying spells" associated with slight cough and "wheezing." She continued to do well until two weeks before admission when she "caught a cold." Cough, anorexia, and fever became progressively worse.

On admission she was moderately ill, had a hoarse cough, and temperature of 39.3° C. The nasopharynx and middle ears were acutely inflamed, and there was postnasal discharge. Many moist râles were heard over the lower right lung field. A systolic murmur and thrill was maximal over the third left interspace and transmitted over the entire precordium. Roentgenograms revealed increased hilar markings with patchy consolidation in the lower right lung field. The pulmonary conus was prominent, and the heart seemed slightly enlarged. She was treated with sulfadiazine and recovered rapidly. She was admitted to the hospital on three subsequent occasions with diagnoses of pneumonia and interventricular septal defect. Between hospital admissions she was treated for recurrent attacks of bronchitis or bronchopneumonia. During this time she had a tonsillectomy, adenoidectomy, and several sinus irrigations in an effort to prevent further respiratory infections.

At the age of 4 years, she was readmitted with the diagnosis of bronchopneumonia. Examination revealed marked nasopharyngitis. Many râles were heard over both lung fields. The cardiac findings were as previously noted. Blood pressure was 102/66. Electrocardiogram revealed left axis deviation. The respiratory infection subsided following sulfonamide and penicillin therapy. Esophagrams (Fig. 1) revealed bilateral indentations of the esophagus in the posteroanterior view with the greater indentation on the left. The right anterior oblique view (Fig. 2) revealed a filling defect in the posterior wall of the esophagus, and in the left anterior oblique view (Fig. 3) there was a similar filling defect with marked anterior displacement of the esophagus. Tracheograms (Figs. 4 and 5) showed uniform constriction of the trachea just above the carina. A diagnosis of anomalous constricting vascular ring was made and an operation performed. A double aortic arch was found encircling the

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†Deceased.



trachea and esophagus. The right arch, which lay in a posterior position, was small but patent. The innominate, left common carotid, and left subclavian arteries arose from the left arch, which lay anterior to the trachea and esophagus. The smaller vessel was ligated and excised, and immediately the freed trachea and esophagus swung toward the right. The postoperative course was uneventful. Esophagrams made postoperatively showed the esophagus markedly deviated toward the right with a filling defect on the left side (Fig. 6). The



Fig. 1—Posteroanterior esophagram (preoperative), showing bilateral constriction of the esophagus

posterior indentation was still noted, but no obstruction to the barium stream could be demonstrated (Fig. 7). The trachea also was deviated toward the right (Figs. 8 and 9); the constriction was as previously noted. Examination of this patient nine months later revealed that she was doing very well and had had no further respiratory infections. The precordial murmur and thrill noted preoperatively persist unchanged.

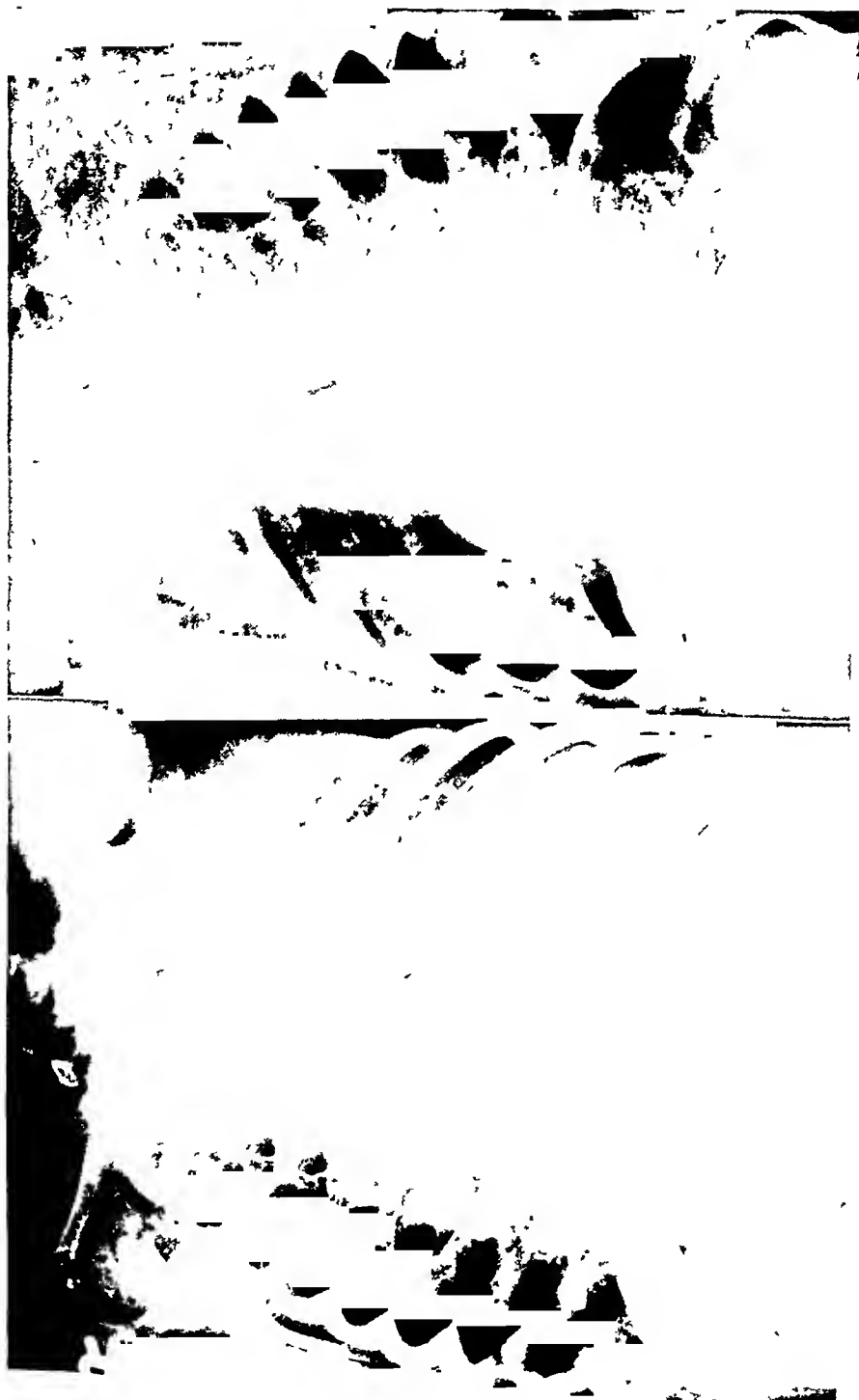


Fig. 2

Fig. 2—Right anterior oblique esophagogram (preoperative), showing both anterior and posterior constriction of the esophagus.

Fig. 3

Fig. 3—Left anterior oblique esophagogram (preoperative), showing marked anterior deviation of the esophagus.



Fig. 4.

Fig. 4.—Posteroanterior tracheogram (preoperative) with the bronchoscope in place. There is definite bilateral constriction of the trachea just at the end of the bronchoscope.

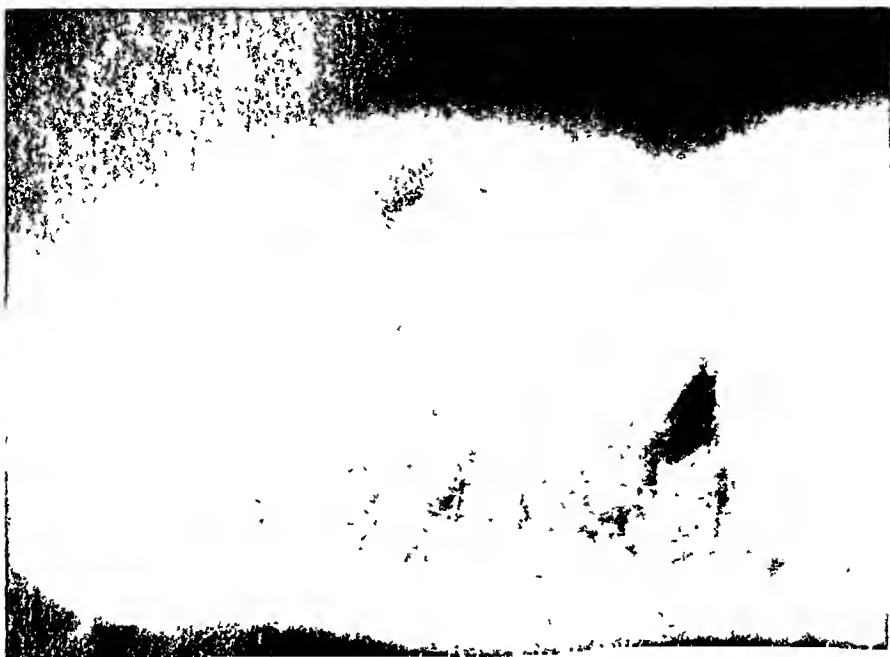


Fig. 5.

Fig. 5.—Right anterior oblique tracheogram (preoperative), showing constriction and anterior displacement of the trachea.



Fig. 6.

Fig. 6.—Posteroanterior esophagram (postoperative), showing the esophagus deviated to the right.



Fig. 7.

Fig. 7.—Right anterior oblique esophagram (postoperative), showing complete filling of the esophagus following cutting of the constricting vascular ring.



Fig. 8.

Fig. 8.—Posteroanterior tracheogram (postoperative), showing that the trachea is deviated sharply to the right. Some constriction of the trachea can still be seen.  
 Fig. 9.—Right anterior oblique tracheogram (postoperative). Narrowing of the trachea can still be noted.

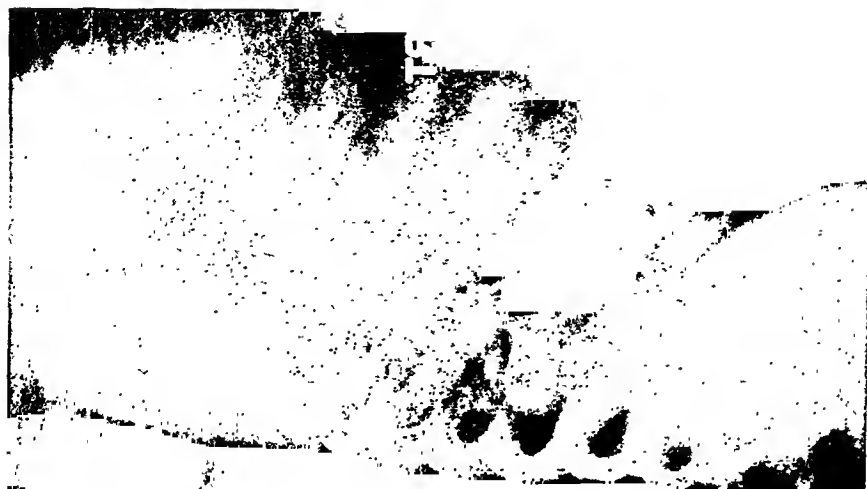


Fig. 9.

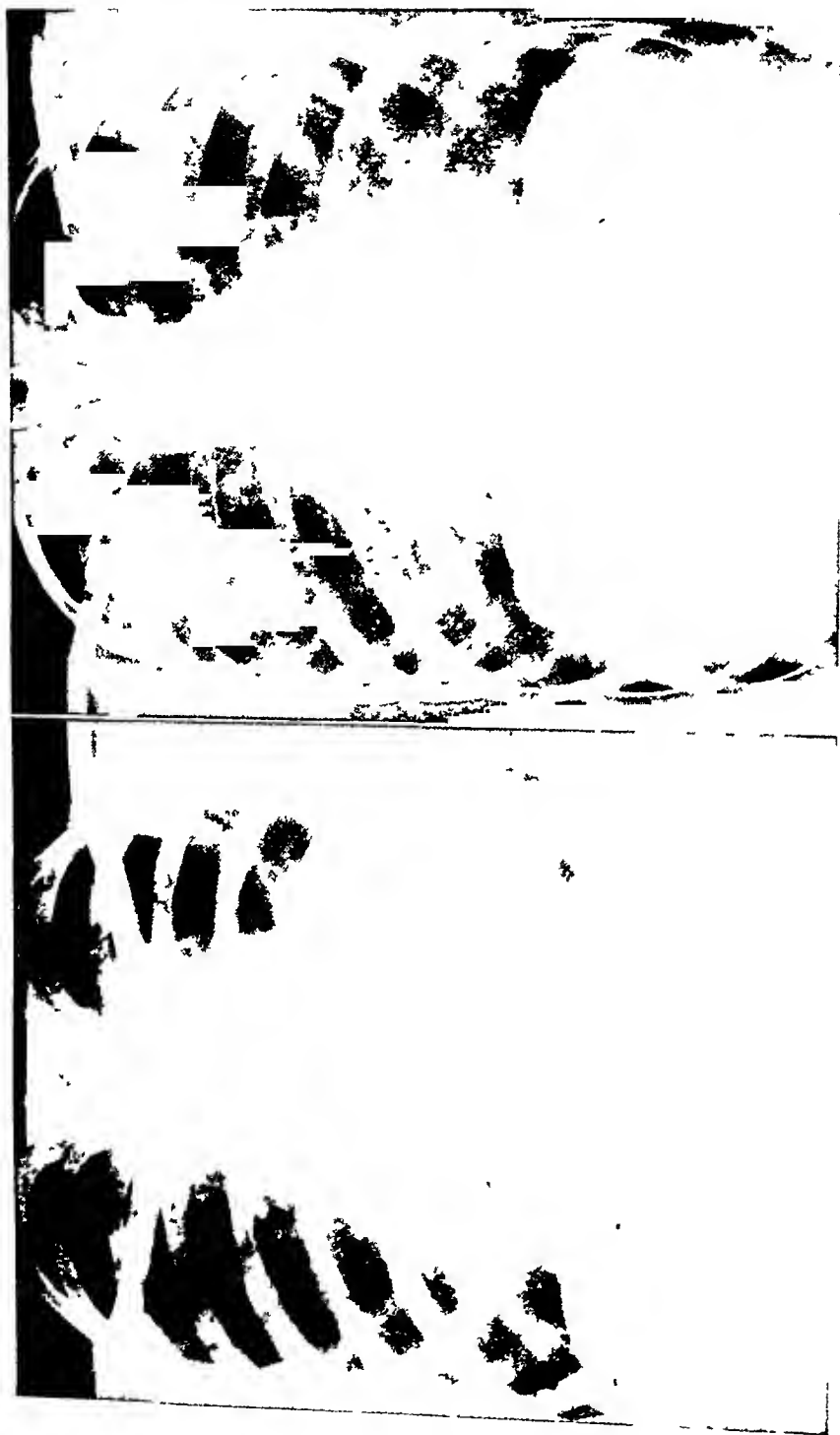


Fig 10

Fig. 10—Posteroanterior roentgenogram of chest which shows evidence of pneumonia in both lung fields. The heart shadow seems slightly enlarged.

Fig 11

Fig. 11—Posteroanterior esophagram, showing obstruction of the esophagus. The heart shadow seems slightly enlarged.

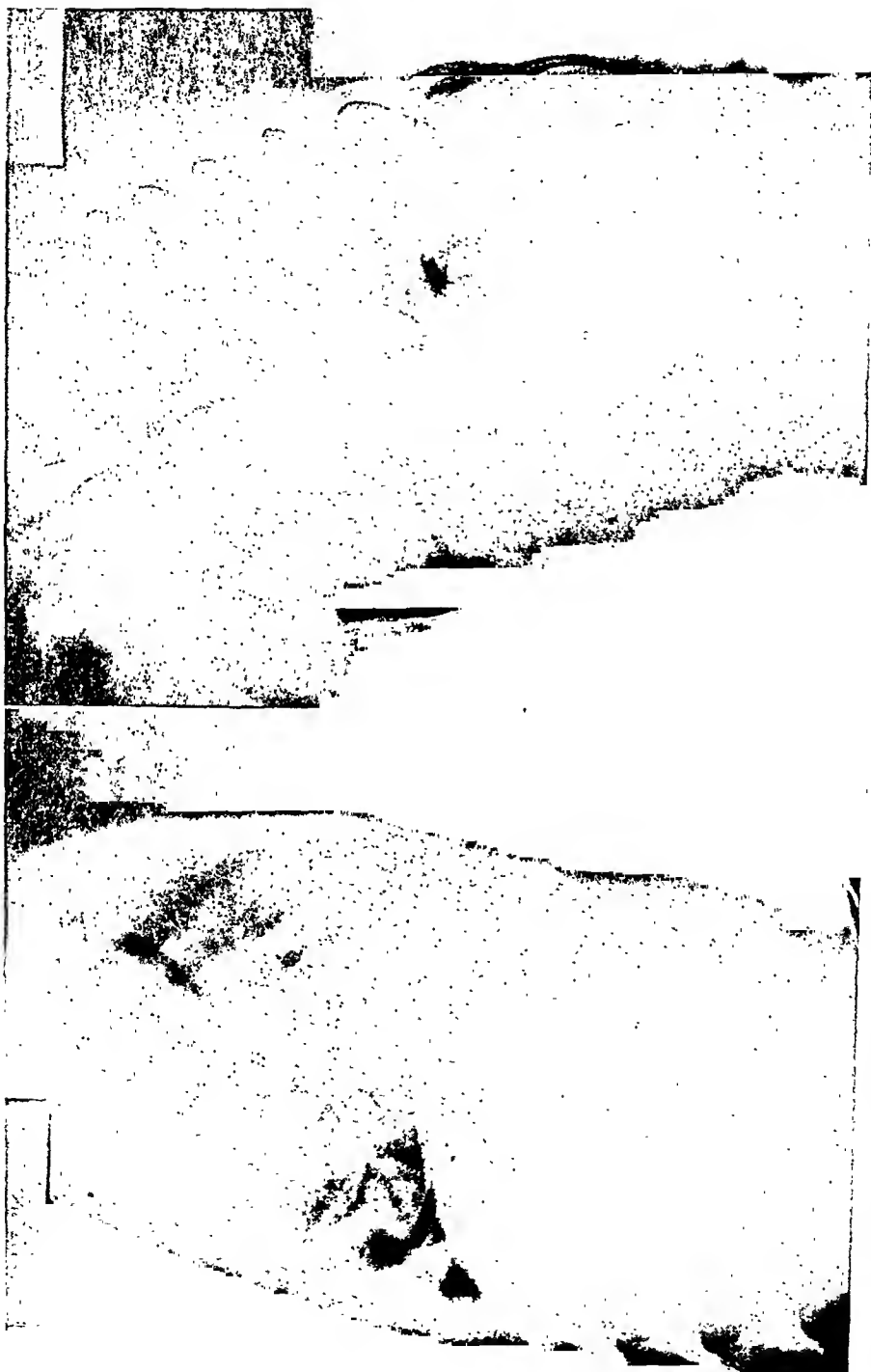


Fig. 12.

Fig. 12.—Right anterior oblique esophagogram, showing narrowing and anterior displacement of the esophagus.

Fig. 13.

Fig. 13.—Left anterior oblique esophagogram, showing narrowing and anterior displacement of the esophagus.

CASE 2.—M. E. R., a 6½-year old white female, was hospitalized because of recurrent attacks of severe bronchopneumonia. The child was known since early infancy to have had congenital heart disease and had been kept on moderately restricted activity. She had done well until about 10 months of age when she developed a croupy cough associated with fever. Recovery was prompt. Since that time respiratory infections were frequent, especially during the winter months. These were always of long duration, associated with fever and a persistent nonproductive cough. During none of these attacks was cyanosis observed.



Fig. 14—Left anterior oblique tracheogram, showing some narrowing of the trachea.

Physical examination on admission revealed a tall white female of 6½ years in marked respiratory distress. Tachypnea was severe, but there was no orthopnea. Faint cyanosis of the nailbeds and lips was observed. The pertinent physical findings were limited to the cardiovascular-respiratory system. Suprasternal inspiratory retraction accompanied the tachypnea. There was questionable impairment of resonance over the right chest anteriorly. The breath sounds were extremely harsh over the left chest, and numerous inspiratory râles were heard. There were, in addition, scattered musical rhonchi over both lung fields during the expiratory phase. A diffuse apex impulse was palpable in the fourth interspace in the midclavicular line. The cardiac rhythm was regular; tones were of good quality. There was a loud systolic murmur over the third and fourth left interspaces transmitted down the left parasternal line and toward the apex. The pulmonary second sound was markedly accentuated. On fluoroscopy the left lung field was seen to be diffusely infiltrated, and an



area of infiltration was seen to extend laterally from the right heart margin toward the right diaphragm. The heart contour was distinguished by considerable increase in transverse diameter and by a bulge to the right which probably represented the right auricle. The left margin was full. On the right there was a moderately dense shadow extending upward from the heart border which was thought to represent pneumonia in an azygos lobe or the superior vena cava (Fig. 10). Fluoroscopic examination with esophagrams in the posteroanterior view revealed a high obstruction of the esophagus (Fig. 11). At the level of the third or fourth thoracic vertebra there was a posterior indentation of the esophagus (Figs. 12 and 13). The location of the descending aorta could not be clearly distinguished. There was marked hilar congestion. The blood pressure in the left arm was 126/70, in the left leg 150/90.

The pneumonia resolved, and with its resolution a thrill became palpable in the fourth left interspace 2 cm. to the left of the midsternal line. This thrill was transmitted over the body of the heart. Repeat fluoroscopic examination verified the impression of an anomalous vascular ring causing compression of the esophagus and trachea (Fig. 14). Operation was advised but refused by the parents. Since discharge from the hospital the patient has continued to experience repeated attacks of bronchopneumonia.

#### COMMENT

Respiratory obstruction and dysphagia lusoria are the two symptoms commonly ascribed to the presence of a constricting anomalous vascular ring, whether this obstruction be due to a double aortic arch, a left arch with right descending aorta, a right arch with left descending aorta, or anomalous origin of the subclavian or carotid arteries.<sup>8-10</sup> Although patients possessing such anomalies are prone to develop recurrent attacks of pulmonary infection, it has been stated that with increased age and increased rigidity of the trachea, compression assumes less significance, and these symptoms tend to disappear.<sup>7</sup> It would, nonetheless, seem that in patients who are suffering severe recurrent attacks of pulmonary disease, relief of the obstruction by surgical intervention might greatly increase the general well-being of the patient by preventing the development of bronchiectasis or other complications of repeated pulmonary infection.

It is suggested that anomalous vascular rings might predispose to pneumonia by causing narrowing of the trachea by external pressure. There may be annular constriction by a vascular ring, or compression and angulation may be limited to one or two sides of the trachea. In either case there may be interference with proper drainage from the tracheobronchial tree. In those situations, such as Case 1, in which the minor limb of the vascular ring is located dorsal to the esophagus, removal of this limb would tend to eliminate both the tracheal constriction and angulation. In the more common situation where the major vessel occupies the dorsal position,<sup>11</sup> relief of the constricting ring may tend to alleviate symptoms in spite of the persistence of the retrosophageal aorta. Postoperative tracheograms in Case 1 showed evidence of continued narrowing of the trachea although the constricting ring had been removed. It is probable that this narrowing will persist for some time inasmuch as growth of the cartilaginous rings has been impeded by the vascular constriction. With early relief of the constriction these rings may grow normally, and the tracheal stenosis gradually disappear.

Because angulation of the trachea and its constriction by a vascular ring may constitute a mechanical obstruction to proper drainage of the pulmonary

tree, visualization of the trachea and esophagus by means of contrast media should be undertaken in all patients having recurrent attacks of pulmonary infection.

Surgical relief of the extrinsic tracheal compression so demonstrated may decrease the number of recurrences of pulmonary infections and prevent the development of pulmonary complications.

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## SUDDEN AND UNEXPECTED NATURAL DEATH

### IV. SUDDEN AND UNEXPECTED NATURAL DEATH IN INFANTS AND YOUNG CHILDREN

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SUDDEN and unexpected natural death challenges the community in many ways. It is as if a hidden enemy were picking and striking its victims without warning, a tactic extremely disconcerting to physicians accustomed to premonitory syndromes. The laity reacts with doubt about the efficiency of the medical establishment and the standards of the public health. Too often both groups approach the investigation of the problem with an offended *amour-propre* which makes its solution doubly difficult. Not infrequently, in the attempt to appease the intellectual doubt, minor findings are magnified, or, worse still, others are unwittingly concocted out of thin air.

In older persons, unexpected death (its suddenness is of secondary importance) usually has a substrate of obvious organic change. True, that substrate may be misinterpreted, but, nevertheless, it exists. In infants and young children (under 10 years of age) its existence is often anything but obvious, and it is because of this cryptic character that the maximum caution should be exercised in the interpretation and evaluation of premortem and necropsy findings. Bacteriologic data may offer pitfalls, unless they are closely scrutinized before placing them in the diagnostic scales.

The material in this presentation is chiefly from the files of the Office of the Chief Medical Examiner, New York City, and it is to Dr. Thomas A. Gonzales, Chief Medical Examiner and his staff, especially Dr. Milton Helpern, a Deputy Chief Medical Examiner, that thanks are due. Illustrative cases also were furnished by the department of pathology of the Saint Joseph Hospital, Fort Wayne, Ind. It should be emphasized that the cases discussed here are those of medicolegal significance. Sudden and unexpected natural death in the hospital population, where there are no suspicious circumstances or anamnestic evidence of previous trauma, is excluded.

In 1945 Helpern and Rabson<sup>1</sup> published the first of a series of reports on sudden and unexpected natural death. That paper was based on a study of 2,030 cases in which autopsy had been performed from Jan. 1, 1937, to June 30, 1943. Its value was enhanced by the fact that age and sex distribution of disease was related to the same factors of the general population. Other studies were devoted to coronary arteriosclerosis,<sup>2</sup> and to spontaneous subarachnoid hemorrhage.<sup>3</sup>

Parenthetically, Potter<sup>4</sup> emphasizes that sudden and unexpected natural death is very uncommon in the neonatal period. There is ample testimony at

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birth to indicate which infants are likely to succumb in the first week or two of life. Turning to infants and young children, it was recorded that those under 5 years of age made up 4 per cent of the population of Manhattan Island in 1940, and that those between 5 and under 10 years, 5.2 per cent (Table I). Although in the first age group males outnumbered females 2.7 per cent to 2.0 per cent, in the second half of the first decade of life the sexes were equally represented, 2.6 per cent each.

TABLE I. PERCENTAGE COMPOSITION OF POPULATION OF MANHATTAN, 1940, AND OF 2,030 CASES OF SUDDEN AND UNEXPECTED NATURAL DEATH FROM BIRTH TO 10 YEARS OF AGE

SEX	BIRTH—4 YEARS	5-9 YEARS
	(%)	(%)
Population, total of:		
male	2.7	2.6
female	2.0	2.6
total	4.7	5.2
Sudden and unexpected natural death, total of:		
male	1.95	0.5
female	0.5	0.0
total	2.45	0.5
Nervous system:		
male	0.1	0.1
female	0.0	0.0
total	0.1	0.1
Cardiovascular system:		
male	0.05	0.0
female	0.2	0.0
total	0.25	0.0
Respiratory system:		
male	1.7	0.34
female	0.2	0.0
total	1.9	0.34
Digestive system:		
male	0.1	0.05
female	0.1	0.0
total	0.2	0.05

The reason for this leveling-off of an initial sex disparity is to be found in the same table (Table I). During the first 5 years, four times as many boys as girls (1.95 per cent; 0.5 per cent) died. Although the percentage of the 2,030 cases in the 5- to 9-year age group fell to 0.5 per cent from the 2.45 per cent of the first half-decade, the sex-mortality disparity was worse than ever; no girls were counted among the very few cases of sudden and unexpected death in this period of life. Here was another confirmation of the often-remarked "lethality" of boy babies.<sup>5</sup>

Unexpected natural death in infancy and childhood, then, is chiefly a phenomenon of male children, helping to overcome the initial preponderance of male over female births. Secondly, this type of death is rare after infancy and young childhood, as proved by the fact that, of a group of sixty-nine patients under 5 years of age studied in greater detail, only six were 2 years or over. Survival beyond the third year of life indicates a very low probability of sudden and unexpected natural death. The lowest probability of this type of death, incidentally, is in the 10- to 14-year category, rises in the next half-decade, and becomes medically significant with the onset of the third decade of life.<sup>1</sup>

Apart from sex disparities, there are differences between races, which must be very carefully interpreted in light of the low economic status of the Negro. Negroes, like the whites, furnished their contribution to the general total of 2,030 cases of sudden and unexpected natural death in almost the same ratio as their share of the population, 15.2 per cent and 15.8 per cent, respectively.<sup>1</sup> In the period of infancy and young childhood up to 5 years of age, however, this race ratio was disconcertingly upset, with five Negroes to every 6 whites (Tables II and III). The general sex ratio was, nevertheless, maintained, with 4 deaths among males for 1 among females. The disturbed race ratio, in view of the unaltered sex ratio and the general race ratio for all ages, suggests that the undue mortality among Negro babies is not inherently racial.

TABLE II. CAUSES OF SUDDEN AND UNEXPECTED NATURAL DEATH IN SEVENTY-THREE PATIENTS UNDER 10 YEARS OF AGE

<i>Respiratory System.</i> —	
Acute bronchitis; bronchopneumonia (see Table III):	White, 19 cases, Negro, 24 cases
Bronchiectasis:	Negro, 8 mo.
Asphyxia (laryngeal inflammation):	White, 3 yr., Negro, 3 yr.
Lobar pneumonia, with empyema:	White 1½ yr.
<i>Gastrointestinal System.</i> —	
Appendicitis with peritonitis:	White, 2 yr., Negro, 4 yr.
Enteritis (salmonella):	Negro, 4 mo., Negro, 1 mo.
Intussusception:	White girl, 3 mo.
Peritonitis, secondary to sepsis (cause undetermined):	Negro, 16 mo.
<i>Nervous System.</i> —	
Meningitis, meningococcal:	White, 2 yr.
Meningitis, tuberculous:	White, 5 yr., Negro, 8 yr.
Hydrocephalus:	White, 1 yr.
Brain tumor:	White, 9 yr.
Pachymeningitis hemorrh. interna:	Negro, 3 mo.
<i>Cardiovascular System.</i> —	
Cardiac myxoma:	White girl, 41 days
Congenital cardiac anomaly:	White girls, 1 mo., 2½ mo., White, 3 mo.
Acute pericarditis in pneumonia:	White girl, 1½ mo.
<i>Miscellaneous.</i> —	
Anaphylaxis:	White, 6 mo., White, 4 yr.
Acute glomerulonephritis:	Negress, 2½ yr.
Unknown:	White, 2, 3, 4, 6 mo., White girl, 14 mo., Negro, 1 mo.*

\*At necropsy, classified under other categories, but reclassified after microscopic, bacteriologic, or chemical examination.

TABLE III. ANALYSIS OF FORTY-THREE CASES OF SUDDEN AND UNEXPECTED NATURAL DEATH FROM ACUTE BRONCHITIS AND BRONCHOPNEUMONIA IN CHILDREN UNDER 10 YEARS OF AGE

AGE	MALE		FEMALE	
	WHITE	NEGRO	WHITE	NEGRO
Under 1 week of age	1			1
1 week—under 2 weeks		2		
2 weeks—under 1 mo.	2	2		2
1 mo.—under 2 mo.	2	1		
2 mo.—under 3 mo.	7	5		1
3 mo.—under 6 mo.	1	5	1	
6 mo.—under 9 mo.	1			
9 mo.—under 1 yr.	2	2		
1 yr.—under 2 yr.		2		
Over 2 yr.		1	1	
		(5 yr.)	(2 yr.)	
Total	17	20	2	4
Total male and female	37		6	
Grand total	43			

Unexpected natural death in infants and young children, especially the former, seems to be caused by diseases of the respiratory system in almost 80 per cent of the cases. In the respiratory group, "acute bronchitis" or "bronchopneumonia" was the diagnosis recorded 9 times out of 10. These diagnoses, as in most of the 2,030 cases of the entire survey, were made without microscopic study. When the latter was done, the original diagnosis was usually substantiated, but there was a small number in which another cause of death was then ascertained. Less often, however, a satisfactory cause of death could not be established (Table II: "Unknown"). In comparison to bronchitis and bronchopneumonia, other forms of respiratory disease are few (Table II).

There are no cases in the series under consideration classified as "asphyxia by overlying." Although that condition is too often the figment of imagination of an overwrought parent, it must be admitted that some infants do asphyxiate. Werne and Garrow<sup>6</sup> have well discredited the abuse of that diagnosis, but in so doing have perhaps overemphasized the role of acute respiratory infection as the correct cause of death. It is not too difficult to imagine an infant with incipient respiratory infection having a convulsion, and then asphyxiating because the convulsion appeared while the child was face down in the crib or was "oversheltered" in the folds of the bedclothes of the parent. Had the baby been supine or free of incumbrances, it might have survived the convulsive seizure. It must also be admitted that the evaluation of the lethal role of the respiratory malady, as judged by microscopic criteria,<sup>7</sup> is not an easy one. It is tempting to give much weight to physical changes in preference to what is at present an equivocal diagnosis of "status lymphaticus." That temptation must be equally resisted because once a case is placed in the cubbyhole reserved for "respiratory disease," its later exhumation and re-evaluation will be doubly difficult. The medicolegal worker ought not fear announcing that he cannot give the cause of death; "an act of God," although not found in the volumes on medical nomenclature, at least has its value in indicating that the physician could not establish the lethal factor or factors.

In comparison to bronchitis and bronchopneumonia, other forms of respiratory death are few (Table II). The finding of gastric contents in the trachea or bronchi of infants too often results in the diagnosis of "asphyxia by inhalation of vomitus" as a primary cause of death. Such findings are not uncommon, whatever the cause of death, but are often recognized in failure of the respiratory apparatus. They are terminal phenomena provoked by the anoxia of the basic condition, whatever the latter may be. The aspiration of vomitus may complete the lethal circle of an obscure primary condition; this, then, raises the possibility of a nonfatal outcome had the aspiration not taken place. Simpson<sup>8</sup> emphasizes the terminal character of the vomitus inhalation, and also warns that "many air-passage fluids . . . might ineautiously be described from their naked eye appearance as inflammatory."

The gastrointestinal tract (Table II) is not a common site for lethal disease. Important, however, was the diagnosis of acute appendicitis with peritonitis as a cause of unexpected natural death. As an example, a boy of 2½ years had persistent vomiting for five days, and died after five hours in the

hospital. There was a questionable history of the ingestion of rat poison containing fluoride. The attending physician was unaware of the symptoms of fluoride intoxication nor did he attempt to determine another cause for the child's symptoms. There were other instances in which children were thought to have taken rat or roach poison, and to which the signs of a rapidly fatal illness were ascribed. Gastric lavage to facilitate chemical examination of the washings may expose the nonpoisonous character of the illness.

Among the relatively few maladies of the nervous apparatus was meningitis. In one, caused by the meningococcus, the 2-year-old boy had fallen several days before death, which came after twelve hours of drowsiness and vomiting. Tuberculous meningitis may be equally rapidly fatal. A Negro aged 8 years ate lunch at school and became ill in the midafternoon with what was called a "cold" and diarrhea. The condition failed to improve, the child became comatose, and died thirty-six hours after the onset of his complaints. A cerebral spongioblastoma in a 9-year-old white boy was associated with neckache for two weeks antemortem. Later he had difficulty in retaining food without vomiting, and died suddenly at home. Internal hemorrhagic pachymeningitis with cerebral compression carried off a 3-month-old baby who had been ailing since his premature birth. Birth trauma was probably the initiating cause.

In the cardiovascular category, not in the New York material, is the case of a white boy who died suddenly at home at the close of his ninth birthday party.<sup>9</sup> On awaking that day, he spoke of a transient pain in the left shoulder, and appeared to be less active than usual. Necropsy uncovered a large, fresh embolus in the pulmonic valve and adjacent part of the main artery, and a partly organized, older embolus in the left pulmonary branch. There was early infarction of the apex of the left upper pulmonic lobe.

Investigation uncovered an interesting history. Six months before he was admitted to the hospital with fever and cough. Neither on physical nor radiologic examination was there evidence of pneumonia. Within a few days pain appeared in the right groin, aggravated on extension of the thigh. There was also tenderness, slight swelling, and prominence of the superficial veins in the area. Later, the left side was similarly involved. A definite diagnosis was not made despite resort to various examinations. Convalescence was not rapid. A month antemortem the child was treated for "pneumonia" of the base of the right lung.

The autopsy explained the premortem story. The proximal part of both femoral and external and common iliac veins, as well as the end of the inferior vena cava, were scarred and had lumens of greatly reduced caliber because of antecedent thrombophlebitis. The fatal embolus took origin from the distal part of the vena cava. The so-called pneumonia of the right lung was provoked by an area of infarction.

There is a group in which a definite cause of death could not be made (Table II), although such cases might be enrolled on gross examination in any category, usually that of the respiratory diseases. In this group there is the temptation to attribute death to "status lymphaticus," especially if the thymus is considered large. A 2-month-old male infant of a well-to-do family had been

in excellent health. At 10 A.M. the child had taken the bottle well, and nothing untoward was noted. While in the carriage on the street, less than three hours later, the baby did not seem "right" to the nurse. She picked up the child, who regurgitated, and then replaced him in the carriage. By the time she arrived at the house, the infant was dead. After complete autopsy, including microscopic study, the anatomical findings were insufficient to explain the death. The thymus weighed 35 grams and the adrenals were small, but this state was not considered to be the cause of death; the pulmonary picture was likewise inconclusive. Similar cases have been encountered in well-nourished and developed, apparently healthy babies about 4 to 8 months old.

Another example will suffice to illustrate the difficulties of diagnosis. A white boy 6 months old had been examined the day before death, had been found well, and was given 1 c.c. of diphtheria toxoid. The next morning at 6 A.M. he was found lifeless in bed. The thymus weighed 35 grams, the lymphoid apparatus was considered hyperplastic, and the adrenals were described as "hypoplastic"; the lungs were congested. Here, too, no satisfactory lethal agent or process could be described.

What is the natural weight and size of the thymus so that there may be more to go on than the description that "the thymus is enlarged"? Potter<sup>10</sup> gives the average birth weight of that organ as 10 grams. For a body of 250 to 750 grams, the thymus is said to weigh 1.4 grams; for one of 3,750-4,250 grams, 15.3 grams; and for a body over 4,250 grams, the thymus weight is stated to be 12.8 grams. Potter adds a significant clause to her statement of the thymic weight, that "considerable individual variation is found."

A personal review of necropsy protocols for a recent one-and-one-half-year period was done to verify Potter's modifying clause. The individual variation was indeed "considerable." Among the prematurely stillborn, one gram was recorded for 5½ months, 5.5 grams for 7 months, and 6 grams for 8 months. Full-term stillbirths had thymus glands weighing 2, 4, 5 (two cases), 6, 10, 12 (two cases), and 14 grams. Among those full-term babies dying within twenty-four hours after birth the weights were 8, 10, 15 (two cases), and 20 grams. The children living a week or less had thymus glands weighing 2 (two cases), 3 (two cases), 7, and 9 grams. In a child of 2½ months the organ weighed 25 grams, and yet in another of 4 months it weighed only 5.5 grams. Two 18-month-old babies had thymus weights of 8 and 15 grams, respectively. The thymus was 16 grams in a girl of 6 years, and 50 grams in the 9-year-old boy dying of pulmonary embolism.

It seems reasonably clear, then, that a thymic weight of 30 to 35 grams may or may not be significant. Granting that a thymus is enlarged, what is the significance of the enlargement, even when coupled with small adrenal glands? Here Simpson<sup>6</sup> is skeptical to an extreme. According to him, "status lymphaticus is no more than a status, and if we admit, however unwillingly, the possibility . . . that such subjects may die more readily than others of a trivial cause, that does not excuse the failure to find that cause. We should be no more at liberty to say that a person died of flat feet or a dwarf stature or some other status."



An enlarged thymus may be the cause of death, rarely as that may happen. A recent necropsy, performed by Helpern and Schneider<sup>11</sup> does illustrate that possibility. A Chinese baby girl of 5 months had been placed on her side in the crib at 1 P.M. Two hours later, the child was found dead in the same position, with no disturbance of clothes or bedding, the head uncovered, and the air-passages unobstructed. The thymus was enormously enlarged, covering the entire mediastinal area and encroaching upon both lung fields. It weighed 77 grams! The adrenal glands were hypoplastic (2.82 grams). Dissection of the trachea uncovered a distinct anteroposterior compression and luminal narrowing. There were asphyxial hemorrhages beneath the pleura and epicardium, and in the thymus. When one recalls that all stenoses are of severer degree during life than after death, the diagnosis of asphyxia by enlarged thymus appears justified. Why the fatality took place when it did, and not a week before or a day later, was not revealed, any more than the time of death can be satisfactorily explained on an anatomic basis in sudden death from occlusive coronary arteriosclerosis without fresh thrombosis or infarction.

#### SUMMARY

Sudden and unexpected natural death in infants and young children encountered in medicolegal practice is chiefly found in male subjects and seldom beyond the age of 3 years. Of a group of sixty-nine patients under 5 years of age studied in detail, only six were older than 2 years of age. The contribution of Negroes goes far beyond their proportion of the population, and is not regarded as a purely biologically racial phenomenon.

Respiratory disease is the great leveler, accounting for almost 80 per cent of the unexpected deaths in infants. Caution may be necessary, however, less undue weight be placed on the role of anatomically minor inflammatory changes in the breathing apparatus.

There is a group of sudden and unexpected natural deaths in which the present usual means of investigation fail to uncover the cause of death. Such cases are encountered in apparently normal infants, usually between the ages of 4 and 8 months.

The role of the thymus has yet to be clarified in the production of unexpected death. The variability of its weight, especially in the newborn infant, makes an evaluation of the lethal role of size alone exceptionally difficult. A single instance of a thymus sufficiently enlarged to have pressed upon the upper airway is recorded, but there was no evidence to indicate why the child died when it did, and not sooner or later.

A plea is made for complete necropsy, including bacteriologic and chemical examination, for judicious evaluation of necropsy evidence and correlation with the clinical history, and for a willingness to admit inability to fix the cause of death.

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## PNEUMONIA IN INFANCY CAUSED BY FRIEDLÄNDER'S BACILLUS

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**B**RONCHOPNEUMONIA in infancy due to Friedländer's bacillus (*Klebsiella pneumoniae*, *Bacillus mucosus capsulatus*) is apparently uncommon, as only a few cases have been reported in the literature. Etienne<sup>1</sup> and Comba<sup>2</sup> have each reported a case. Comba's case was that of an infant 6 days old in whom pneumonia was found at necropsy; pure cultures were obtained from the blood and lungs. In 1915 Dunn and Hammond<sup>3</sup> reported the case of a 14-month-old infant who had "Friedländer pneumonia," the diagnosis being made by accidental lung puncture during a thoracentesis for effusion.

Kliewe<sup>4</sup> in 1930 reported an epidemic among infants in an institution. He felt that in his cases the Friedländer's bacillus had to be regarded as the primary cause since it had been found in the throats of all of his patients as well as in the lungs of several at autopsy. A search for other agents, especially influenza bacilli and pneumococci, was unsuccessful. Moreover, the infection had spread from a child who had contracted pharyngitis caused by Friedländer's bacillus. Several days later "catarrh" and pneumonia were contracted by eleven of the twelve children sleeping in the same ward. Friedländer's bacillus was found in the throats of eleven of these patients. One child died of severe pneumonia and the same organism was found in the lungs. Examination of the other children (about 100) in this institution revealed Friedländer's bacillus in the throat of only one child.

Ferguson and Tower<sup>5</sup> in 1933, presented the case of twins, one of whom died, in which instance the bacillus was isolated from the lungs and trachea post mortem. The twin brother became ill five days later with pneumonia and a throat culture revealed a pure culture of Friedländer's bacillus. This patient recovered, as did the infant reported by Miller, Orris, and Taus.<sup>6</sup> Their patient also had a pure culture of Friedländer's bacillus obtained from the nose and throat. The diagnosis was based on the insidious onset of the infection, the therapeutic ineffectiveness of penicillin and sulfadiazine, the prompt response to streptomycin, the positive cultures, and the x-ray appearance of several thin-walled cavities in the lungs which decreased in size as the patient improved.

Although *K. pneumoniae* may be present in the respiratory tract under normal conditions,<sup>7</sup> may be found along with *Hemophilus influenzae* and *Hemophilus pertussis* in chronic rhinitis in children,<sup>8</sup> and may at times be found in infections of the sinuses and ears,<sup>9</sup> the routine throat cultures done at the Milwaukee Children's Hospital revealed it in pure culture only in those cases showing pulmonary changes.

Its presence in the upper respiratory tract was viewed with suspicion, as a possible contamination or as a secondary invader by Baehr, Schwartzman, and Greenspan,<sup>9</sup> because it was found with much greater frequency in the intestinal tract. Solomon,<sup>10</sup> however, disagreed with this belief.

The diagnosis of "Friedländer's pneumonia" in adults is generally based on the clinical and roentgenologic evidence of pulmonary consolidation. According to Kornblum<sup>11</sup> it shows diffuse patchy consolidations which may coalesce. Typically, in these areas thin-walled cavities and abscesses without walls may form.<sup>12</sup> In infants, however, the roentgen signs, characteristic of the adult disease, may not occur.<sup>6</sup> Also, since the advent of streptomycin the course of the disease has been affected markedly.<sup>13, 14</sup> Moreover, inasmuch as, ante-mortem lung aspiration and urine and blood studies for specific capsular polysaccharides are not practical in infants, the bacteriologic observations on nasopharyngeal smears and cultures and blood cultures constitute the important diagnostic features in these cases.

The purpose of this paper is to present seven cases of pneumonia in which the Friedländer bacillus was isolated as the sole or predominant organism.

#### CASE REPORTS

CASE 1.—G. S., a 3-month-old male infant, was admitted on Feb. 2, 1948. The child had a cold with cough for two weeks, but had had no fever until admission, when the temperature was 104° F. The child was placed on penicillin and symptomatic treatment. An admission x-ray revealed normal heart and lungs. The throat and nasopharyngeal culture showed only staphylococci. The patient ran a febrile course with a temperature of 100 to 104° F. for about ten days. At this time x-ray revealed bronchopneumonia. He continued to cough and have respiratory difficulty, the throat repeatedly filled with mucus, and there was a short attack of diarrhea. Because of the failure to improve, another throat culture was performed which revealed Friedländer bacilli in pure culture. Sulfadiazine was started and penicillin discontinued, and within two days the temperature fell to normal. The chest cleared slowly and the patient was discharged, recovered, sixteen days after admission.

Laboratory.—Urine showed one plus albumin with occasional white blood cells. The admission blood count was 7,850 leucocytes with 55 per cent neutrophils, 36 per cent lymphocytes, 10 Gm. hemoglobin per 100 c.c., and 4,950,000 red blood cells. The Kline test was negative, as was the Mantoux (1:1,000). Agglutination and precipitin studies on his serum (obtained three weeks after discharge) with antipneumococcus type two serum, with urine from two other patients (Cases 5 and 6) recovered during their acute infection, and with killed Friedländer bacilli were negative.

CASE 2.—M. N., a male infant 3 weeks old, was admitted April 6, 1948. A week prior to admission a nasal discharge and cough were noted, and the day before coming to the hospital diarrhea began. On admission, his temperature was 98° F. per rectum, respirations were rapid and shallow, and cyanosis was present. On physical examination there were signs of early consolidation.

His condition appeared critical and he was given large doses of penicillin as well as sulfadiazine. The chest x-ray revealed widespread bilateral bronchopneumonia. The condition remained serious for several days, and when the throat culture revealed a pure culture of Friedländer's bacillus, streptomycin 125,000 units every three hours was prescribed. The patient began to improve clinically within forty-eight hours although râles continued to be heard in both lungs for about eight days and the color remained somewhat cyanotic.

The diarrhea improved with dietary management. Repeated throat cultures just prior to discontinuance of the streptomycin revealed the presence of hemolytic *Staph. aureus*. During the entire course of the illness the child ran no fever. He was sent home upon recovery seventeen days after admission.

*Laboratory.*—The urine showed one to two plus albumin, traces of sugar, and an occasional white blood cell and red blood cell. The admission blood count was 26,000 with 47 per cent neutrophils and 46 per cent lymphocytes, 4,210,000 red blood cells and 14 Gm. of hemoglobin per 100 c.c. The leucocyte count ranged from 19,200 to 26,000 per cubic millimeter, with from 45 to 65 per cent neutrophils. The Kline and Mantoux (1:1,000) were negative. Agglutination and precipitin studies on his serum (obtained three weeks after discharge) with antipneumococcus type two rabbit serum, with urine obtained from patients A. G. and P. M. (Cases 5 and 6) during their acute infection, and with killed Friedländer bacilli from patient P. M., were negative.

CASE 3.—J. L., a 6-month-old female child, was admitted to the hospital on April 8, 1948. The patient had caught cold, and noisy respirations and vomiting were noted four days before admission. These became progressively worse, and she had a convulsion on the day of admission. At that time, she was acutely ill with a rectal temperature of 103.6° F. She was lethargic and had a weak cry. She had a catarrhal otitis and a pharyngitis, and the breath sounds were harsh on both sides. Because of the convulsion and her general appearance, a spinal tap was done. The globulin, sugar, cell count, and culture were normal. Next day râles were heard, and bronchopneumonia was confirmed by x-ray. A small amount of pleural fluid was also noted on x-ray.

The patient was treated with large doses of penicillin, but continued to run a febrile course. The admission throat culture revealed Friedländer's bacillus predominating, and streptomycin was started (one gram a day in divided doses). In addition, streptomycin and penicillin aerosol were given. The fever continued to be elevated, but clinically the patient showed improvement, although by x-ray the extensive pneumonic process with peripheral effusion remained. Another throat culture gave a pure culture of Friedländer's bacillus. For eight days after initiation of streptomycin the irregular febrile course continued. Sulfadiazine was also started. Slowly the chest cleared, as shown by x-ray as well as clinically, and the temperature leveled off. She was discharged as recovered twenty-four days after admission.

*Laboratory.*—The urine showed one plus albumin, with thirty white blood cells per high power field, and many clumps of leucocytes. On discharge it was normal. The leucocyte count was 28,500 per cubic millimeter with 70 per cent neutrophils and 30 per cent lymphocytes, 9 Gm. of hemoglobin per 100 c.c., and 3,690,000 red blood cells per cubic millimeter. Blood culture showed no growth at seven days, and Kline and Mantoux (1:1,000) were negative.

CASE 4.—S. O., a female child, was 6 months old when admitted to the hospital on April 15, 1948. The child had had a cold for several days. The day before admission she had begun to breathe with difficulty and cough, and her temperature rose to 104° F. The child was dyspneic and had a dusky color. Auscultation of the chest revealed moist râles and occasional wheezes on both sides. Shortly after admission the normal admission temperature rose to 101.8° F. and she continued this febrile course for five days. The admission x-rays appeared normal, but despite this, the lungs continued to show râles and rhonchi for five days in spite of penicillin. After the throat culture revealed a pure culture of Friedländer's bacillus, streptomycin therapy was initiated, and within thirty-six hours the fever began to fall and the child began to improve. She recovered and was discharged nine days after admission.

*Laboratory.*—The urine contained some albumin, a trace of sugar, and occasional red blood cells and white blood cells. The leucocyte count was 10,400 per cubic millimeter with 42 per cent neutrophils and 58 per cent lymphocytes. There were 4,280,000 red blood cells per cubic millimeter with 8 Gm. of hemoglobin per 100 c.c.

CASE 5.—A. G., a 7-month-old male infant, was admitted May 9, 1948. He had started to cough five days before admission and developed a slight fever. Wheezing respirations started the day before admission. His temperature was 102° F. and he appeared quite pale. Both eardrums were injected and there was mucus in the throat. Examination of the lungs revealed expiratory and inspiratory wheezes and occasional râles. He was given penicillin but did not improve. His temperature rose to 104° F. and he began to vomit. Throat smear and culture revealed the presence of Friedländer's bacillus. Streptomycin therapy was started and within twenty-four hours the temperature had fallen to normal; he was ready for discharge on the eighth hospital day.

*Laboratory.*—The urine was normal. The initial blood count showed 12,000 white blood cells per cubic millimeter with 59 per cent neutrophils and 41 per cent lymphocytes. There were 4,280,000 red blood cells per cubic millimeter with 8 Gm. of hemoglobin per 100 c.c. A blood culture showed no growth after seven days. The pure culture from the throat did not give a positive capsular stain, so a mouse was injected with the culture. It died within three days and typical Friedländer's bacilli were recovered from the peritoneal fluid. The Kline was negative. X-ray examination of the chest on two occasions revealed only hilar accentuations. Agglutination and precipitin studies with his serum (at time of discharge) and killed Friedländer's bacilli were negative, as were precipitin studies on his urine (obtained during the acute infection) with serum from G. S. and M. N. (Cases 1 and 2).

CASE 6.—P. M., a 13-month-old male infant, was admitted on May 3, 1948. On the day before admission a cold was noted, with wheezing respirations and a slight cough. Physical examination revealed a pale, acutely ill, dyspneic child. There were bilateral râles, and the throat was injected and filled with mucus. X-ray examination of the chest revealed pneumonia, and penicillin and sulfadiazine were given. The next day the temperature rose to 106° F. and he started to vomit and have convulsions. Breathing was difficult and he became cyanotic and appeared moribund. A spinal tap revealed no significant findings except for a trace of globulin and 50 mg. per cent total protein. The fever remained high the next four days and he had periods of apnea and cyanosis in spite of the administration of oxygen. Unconsciousness occurred and there were purposeless movements of the extremities. He had convulsions occasionally during this period. Repeated x-ray examinations of the chest showed extensive bilateral bronchopneumonia, and throat culture, which had shown a mixed flora on admission, revealed at this time Friedländer's bacillus in pure culture. Treatment with streptomycin had been started (one gram a day) three days earlier. For a week he took no oral fluids, was unresponsive, and was fed parenterally or by gavage. He then began to improve.

The eye grounds appeared normal, but he failed to respond to the blink reflex and to light. There was a searching nystagmus, and the arms and legs were markedly spastic with hyperactive reflexes. Neurological consultation was had and the consultants felt that there was diffuse cerebral dysfunction following the extreme toxemia and cerebral anoxia. The carbon-dioxide combining power during the period of high fever and convulsions was 59.7 and 68.3 volumes per cent; plasma chlorides were 479 mg. per 100 c.c.

The child's temperature remained normal for the next ten days, but streptomycin therapy was continued because repeated throat cultures revealed pure cultures of Friedländer's bacillus. He gradually became more alert and now will respond and take feedings. His eye grounds are still normal. Repeated spinal taps show a trace of globulin and 50 mg. per cent protein, but are sterile. Throat cultures even after two weeks of streptomycin, sulfadiazine, and streptomycin-penicillin aerosol continue to show Friedländer's bacillus along with mixed flora. His pneumonia cleared in about eighteen days, but he continues to run a febrile course of 101 to 104° F.

*Laboratory.*—The urine has shown one plus albumin on several occasions but has otherwise been normal. The admission blood count revealed 15,800 white blood cells per cubic millimeter with 81 per cent neutrophils and 10.5 Gm. of hemoglobin per 100 c.c.

Mantoux (1:1,000) and Kline tests were negative. A culture of Friedländer's bacillus obtained from his throat was not agglutinated by his serum, drawn three weeks after the infection was discovered.

CASE 7.—S. B., a one-month-old female infant, was admitted on May 21, 1948. She had been ill for five days with a cold, cough, and fever. The day before admission she had become "ashen in color and had stiffened out." On admission the temperature was 107.4° F. and she appeared moribund. Respirations were rapid and wheezing, with marked substernal retraction. She was cyanotic. Her throat was red and there were fine râles in both lungs. Penicillin, parenteral sulfadiazine, and streptomycin were administered. The temperature fell, but on the following day she began to have convulsions and became cyanotic. A spinal tap was done, showing a faint trace of globulin, 30 mg. per cent protein, and 95 mg. per cent sugar. The blood culture was sterile, but the throat revealed a pure culture of Friedländer's bacillus.

The patient was then also started on streptomycin aerosol. The convulsions, accompanied by cyanosis, were almost continuous for one day. Her condition remained critical, and she was unable to take oral feedings for almost a week, then gradually began to respond. Pedal spasm was noted and spasticity of the lower extremities was present. The pneumonic process gradually cleared. Friedländer's bacilli slowly disappeared from her throat and the temperature fell to normal. At discharge she appeared well except for residual spasticity of the lower legs, which is improving. The last throat culture still showed mixed flora with some Friedländer's bacilli, seventeen days after admission.

*Laboratory.*—Admission blood count showed 20,100 white blood cells per cubic millimeter with 58 per cent neutrophils, and 11 Gm. of hemoglobin per 100 c.c. Urinalysis showed one plus albumin, and 12 to 15 white blood cells per high power field. Her Kline test was negative.

#### COMMENTS

All of these cases presented a rather insidious onset, except Case 6, and all failed to respond to penicillin and/or sulfadiazine, except one (Case 4), but did show prompt improvement after receiving streptomycin, excluding Cases 6 and 7. Moreover, five of the seven patients showed marked pallor and cyanosis, and all had a cough. All had some vomiting and/or diarrhea. However, there did not seem to be any uniformity as to temperature and leucocyte count. All had x-ray findings of pneumonia, except Cases 4 and 5, although none developed the typical picture of abscesses and cysts. However, all received prompt treatment with streptomycin except Case 1, who clinically presented a picture of bronchiolitis rather than a true pneumonia. In these clinical findings the cases presented resembled the three cases of Ferguson and Tower, and Miller, Orris, and Taus closely.

Smears of the throat, in all cases, revealed well-encapsulated, short, plump rods with rounded ends, and all showed a positive capsular stain by Hiss's method, except Case 5. Here the capsule was found only after passage through a mouse. The rods were nonmotile and were gram-negative. A pure culture of the same organism was obtained on blood agar; there being numerous white, convex, smooth, glistening, opaque, slimy colonies. When fished, these colonies were tenacious and stringy, and bore out the statement of Breed, Murray, and Hitchens, namely, "It is often possible to make a tentative diagnosis of the bacillus from the appearance of this growth."<sup>15</sup>

Zinsser and Bayne-Jones<sup>16</sup> do not depend on the fermentation reactions to differentiate the types of Friedländer's bacillus, as a number of carbo-

hydrates are fermented and the reactions are highly variable. They also state that the older work on serologic differentiation of organisms of this group (*B. mucosus capsulatus*) led to no useful conclusion. Klieve,<sup>4</sup> too, reported that countless attempts had been made to set up various types of Friedländer's bacilli by serologic methods, without success. He tried agglutination studies in nine of eleven children sick with Friedländer's pneumonia, using the serum from the patients and pure cultures of the Friedländer's bacillus and other allied groups. The blood had been taken at the end of the second week of illness. His results were equivocal, however, as the serum plus homologous types of Friedländer's bacillus gave positive agglutinations in dilutions from 1:20 to as high as 1:600 in only five of them. He also prepared rabbit vaccines and then used this material in agglutination studies, again with equivocal results. He concluded from these reactions that biochemically and culturally similar groups of Friedländer's bacillus can behave differently serologically, and he felt that although there were various groups of Friedländer's bacillus, the various types could not be sharply distinguished. He concluded from his studies that there were two types of Friedländer's bacillus, an agglutinable and a nonagglutinable type.

Using an agglutination reaction similar to a macroscopic Widal test, we were unable to obtain a positive reaction with serum from clinically well patients and a killed pure culture of Friedländer's bacillus obtained from a patient with pneumonia (Case 6). The precipitin reaction with immune sera as described by Dochez and Avery<sup>17</sup> based on the elaboration of a specific soluble substance which is found in the urine during the course of pneumonia due to Friedländer's bacillus was negative in our cases, as were the cross precipitin reactions between pneumococcus type two antisera and our patient's sera.<sup>18</sup> Both these reactions, however, depend on immune sera corresponding in type to the infecting organism, so that a negative reaction means little, as we were unable to type the causative agent.

All of the surviving cases showed rather rapid improvement after streptomycin treatment was initiated, (except Cases 6 and 7, both of whom had a stormy course). This drug seems to be the one of choice at present.<sup>13, 14, 19</sup> In Cases 6 and 7, the Friedländer's bacillus did not completely disappear from the throat even after the pneumonia had cleared.

#### SUMMARY

Seven cases of atypical pneumonia admitted to Milwaukee Children's Hospital in the spring of 1948 showed pure cultures of Friedländer's bacillus in material obtained from the throat.

Streptomycin was an effective therapeutic agent in all of these cases.

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# A CASE OF AMYOTONIA CONGENITA ASSOCIATED WITH OCCLUSION OF THE SAGITTAL SINUS AND BILATERAL SUBDURAL HYGROMA

## DEMONSTRATION OF OCCLUSION BY DIOTRAST SINOGRAPHY

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OPPENHEIM first described amyotonia congenita.<sup>1</sup> He stated that the main feature of this condition was a marked degree of muscular flaccidity so that there was an extensive range of passive movement at all joints. Although the muscles were flabby there was no local atrophy. There was also a reduction of active movement which varied in degree from case to case and with it there was diminution or absence of tendon reflex. Oppenheim suggested that this was a congenital condition although it might not always be noticed after birth. It was his impression that the condition was due to a delayed or disordered development of the musculature and that there was no disease of the central nervous system. He further stated that in time there was more or less recovery and for this reason there was no right to regard it as a dystrophia musculorum. He originally called the condition myatonia congenita, but since then the name of amyotonia congenita or Oppenheim's disease has usually been given to it.

Lewey summarized the literature to 1941.<sup>2</sup> He stated that the pathogenesis of this condition is still highly controversial despite the reports of thirty-two cases in which necropsy was performed. He quoted Spiller, Lereboullet and Baudouin, Councilman and Dunn, and Silberberg as unable to find pathologic changes in the nervous system. Alterations in their cases were limited to the muscles. "In twenty-six other cases in which necropsy was reported by nineteen authors, pathologic changes in varying degrees were observed in the anterior horn cells, spinal roots and the muscles." He also quoted Bielschowsky, Archangelsky, Nielsen, Rothmann, and Skoog as having expressed the belief that in amyotonia congenita the muscular changes do not follow but parallel the disease of the central nervous system. "The concept of developmental retardation is strengthened by the observation that in some cases of amyotonia congenita the posterior column and the anterior and posterior spino-cerebellar tracts were not myelinated or were not completely myelinated at the end of three months of life, neither was the white matter of the brain in two instances (Bielschowsky). The cortical and cerebellar cells and the cortical architecture were involved in three cases (Bielschowsky, Conecetti, and Conel). Bielschowsky found polygyrous type of cortical convolutions; disturbance of cortical architecture; large lamina II; increased granules in layers 4 and 6; numerous eajal cells in molecular layers; and neuroblasts in myelinocones (2 cases)."

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Lewey concluded that his three cases favored the theory that amyotonia congenita of Oppenheim may occur on the basis of developmental retardation and malformation of unknown etiology.

Burdick, Whipple, and Freeman<sup>3, 4</sup> have reported cases of amyotonia congenita in which the paracentral lobule (motor cortex), showed almost complete absence of the large, multipolar, Betz cells. The cortical architecture of the other areas of the brain were normal. They have concluded that amyotonia congenita originates from a developmental defect which affects both the large pyramidal cells of Betz in the motor cortex and the anterior horn cells of the spinal cord with resulting hypoplasia of the muscle. However, they have offered no theories for this selective involvement of the paracentral lobule.

The writer presents the following case with the hope that it will give a clue to the etiology of this baffling condition in some patients.

#### CASE REPORT

Baby J. S., aged 7 months, was referred on Nov. 15, 1947, by Dr. Harry Rubin. The mother complained that since birth the infant did not move his legs. The arms moved slightly, the cry was feeble, and he had difficulty in sucking. A sister 6 years of age is normal. The family history was negative for a similar condition.

*Obstetrical History.*—The obstetrical history was obtained from Dr. Robert McN. Mitchell:

"Mrs. E. S., age 32, was examined on Aug. 16, 1945. Her general condition was excellent except for extreme nervousness. The Wassermann was negative. The Rh factor was positive and the blood type was O. The red blood count was 3,900,000 and the hemoglobin was 11.5 Gm. or 74 per cent. The mother's course during the next seven months was satisfactory and the weight gain amounted to twenty-four pounds. When she was eight months pregnant a chair was pulled from her and she struck her buttocks on the floor. She was slightly shocked but there was no bleeding. During pregnancy her health was good and she did not have any severe head colds, grippe, or influenza; her diet was adequate. The infant seemed to be normal as to movement in utero although the mother was worried because, 'This baby did not move in my abdomen like my previously normal child.' Mrs. S. was delivered on March 26, 1947, of what appeared to be a normal male infant weighing 7 pounds, 8 ounces. Her labor was not extreme. She was given 3 grains of Secenal for analgesia plus caudal anesthesia using catheter technique. The duration was three hours and the volume of Metycaine was 75 c.c. of 1½ per cent solution. The delivery was low forceps of a normal LOA position. A median episiotomy was performed and the baby cried lustily immediately following delivery."

*The Neurological Examination*—The infant was alert and his eyes followed the examiner. He smiled feebly. The head appeared enlarged in the parietal areas but the circumference was 44.5 cm. The anterior fontanelle was enlarged but not tense (Figs. 1 and 7). The pupils were equal, moderately dilated, and reacted well to light. The external ocular movements were normal and the fundi negative. There was a slight weakness on smiling, particularly on the left side of the face. The deep tendon reflexes were absent. There was a marked hypotonia in all the extremities so that the limbs could be hyperextended at the joints in bizarre positions. There was neither Hoffmann nor Babinski sign. The extremities showed no atrophy. The infant could hold objects placed in his hands but a marked weakness was present. He could not hold up his head and there was only slight movement at times in both lower extremities. He would cry feebly to painful stimuli on any side.

The patient developed pneumonia and was admitted to the neurosurgical service at the Temple University Hospital five days after the above examination. He was seen by Dr. W. N. Nelson who also suggested a diagnosis of amyotonia congenita and, because of the peculiar shape of the head, a subdural tap to rule out a hematoma. Dr. Gilpin considered either Werdnig-Hoffmann's paralysis or amyotonia congenita. The blood count and urinalysis were normal following recovery from the pneumonia. The blood Wassermann was negative. A twenty-four-hour urine specimen for creatinine and creatine with a volume of 284 c.c. was reported as follows: free creatinine, 48.3 mg. per volume; total creatinine, 124.5 mg. per volume, equals 15.9 units. The creatine was 76.2 mg. per volume.



Fig. 1.—Amyotonia congenita in an infant 7 months of age. Note enlarged anterior fontanelle, wide biparietal distance, and position of extremities.

Stimulation of all extremities by faradic and galvanic current on Dec. 4, 1947, showed a very slow response in all muscles. Recheck examination on Jan. 14, 1948, showed a decided slowing of all muscle responses to faradic and galvanic current.

*Muscle Biopsy Reports.*—Biopsy was made on the left gastrocnemius. Grossly the specimen was pale, grayish tissue 0.5 cm. in diameter. Microscopically, the section showed multiple clumps of tiny, underdeveloped, muscle cells both in single and group sections. Throughout the biopsy there were a few hypertrophied fibers. The majority of the muscle fibers showed a poorly developed striation and in some instances the sarcolemma was finely or coarsely vacuolated. The visualized nerve fibers appeared normal. Diagnosis was amyotonia congenita (Dr. A. R. Peale). (See Fig. 2.)

Biopsies were taken of the right gastrocnemius and the left and right deltoid muscles on Feb. 17, 1948. Microscopically the biopsies from the right gastrocnemius and the left deltoid showed only fibrofatty tissue. The biopsy from the right deltoid showed a portion of hypertrophied muscle and several tiny atrophied muscle groups being histologically compatible with the diagnosis of amyotonia congenital. (Dr. W. D. Campbell.)

The skull roentgenogram showed a brachycephalic contour manifested by the reduction of the anterior-posterior diameter of the cranium and an increase in the vertical and lateral diameter. (Dr. George Wohl.)



Fig 2—Muscle biopsy of left gastrocnemius muscle ( $\times 260$  hematoxylin and eosin). Note clumps of tiny undeveloped muscle cells. A few hypertrophied fibers are present.

A bilateral subdural tap was done on Dec. 2, 1947. Thirty cubic centimeters of xanthochromic fluid was removed from the left side and 20 c.c. of air were injected. Sixty cubic centimeters of slightly pinkish subdural fluid were removed from the right subdural space and 50 c.c. of air injected. The analysis of the fluid from the subdural space was as follows:

#### RIGHT SUBDURAL SPACE

Protein, 57 mg. per 100 c.c.  
 Sugar, 56 mg. per 100 c.c.  
 Chlorides, 720 mg. per 100 c.c.  
 Cell count, 2 WBC, many RBC  
 Wassermann, negative  
 Colloidal gold curve, 0000000000  
 Culture, negative

#### LEFT SUBDURAL SPACE

Protein, 400 mg. per 100 c.c.  
 Sugar, 83 mg. per 100 c.c.  
 Chlorides, 680, mg. per 100 c.c.  
 Cell count, no cells  
 Wassermann, not reported  
 Colloidal gold curve, not reported  
 Culture, negative

Roentgenograms following injections of air into the subdural space were reported as follows: "There is a large amount of air in the subdural space,



Fig. 3.—A, Anteroposterior view. B, Lateral view. Roentgenograms showing bilateral subdural hygroma. Some of the hygroma fluid has been removed through a needle inserted into the subdural space and replaced with air. This procedure was done before the encephalogram. Note the fluid level.

particularly on the left side where a fluid level is visualized at the vertex when the patient is examined upright. On the right side a large amount of subdural air is seen over the convex surface of the brain in an unusual manner. There is a large subdural collection over both cerebral hemispheres, it being most marked over the left cerebral hemisphere, and the roentgenographic findings are consistent with the diagnosis of subdural hygroma." (Fig. 3, A and B.)

A spinal puncture was done on Dec. 5, 1947. The pressure was not recorded. Fifteen cubic centimeters of clear spinal fluid were removed. There were no cells. The protein was 22 mg. per 100 c.c.; the chlorides were 720 mg. per 100 c.c.; the Wassermann and colloidal gold curve were negative.

Recheck subdural taps were done on Dec. 14, and Dec. 19, 1947. Forty cubic centimeters of slightly red subdural fluid were removed from the left subdural space and 30 c.c. of air injected, and approximately 10 c.c. of pinkish subdural fluid were removed from the right subdural space and 10 c.c. of air injected. Roentgenograms again confirmed the diagnosis of subdural hygroma.



Fig. 4.—Subdural membrane ( $\times 200$  hematoxylin and eosin, see text.)

In view of the persistent reaccumulation of fluid, a bilateral exploratory trephine was done under local anesthesia on Dec. 26, 1947. Two small incisions were made over both coronal sutures in the prefrontal area. The dura was opened bilaterally, and there was evidence of a transparent subdural membrane on both sides. A specimen of this membrane was removed on the left side,

following which there was an immediate gush of yellowish, slightly blood-tinged fluid. Approximately 40 c.c. were removed. The membrane appeared less than one millimeter in thickness. A similar condition was present on the right side except for less subdural fluid. A small specimen of prefrontal cortical and subcortical tissue was removed and a silver clip was applied to the cortex for future x-ray identification. The incision was then closed.

The infant showed no untoward reaction from this procedure. The tissue labeled left and right subdural membrane showed a general picture of fibroblastic proliferation and tiny areas of pigmentation. Diagnosis was subdural membrane (Fig. 4). Section of the brain tissue showed a paucity of neuron cells, collection of glial cells, and spotty areas of vacuolation suggesting encephalomalacia (Fig. 5).

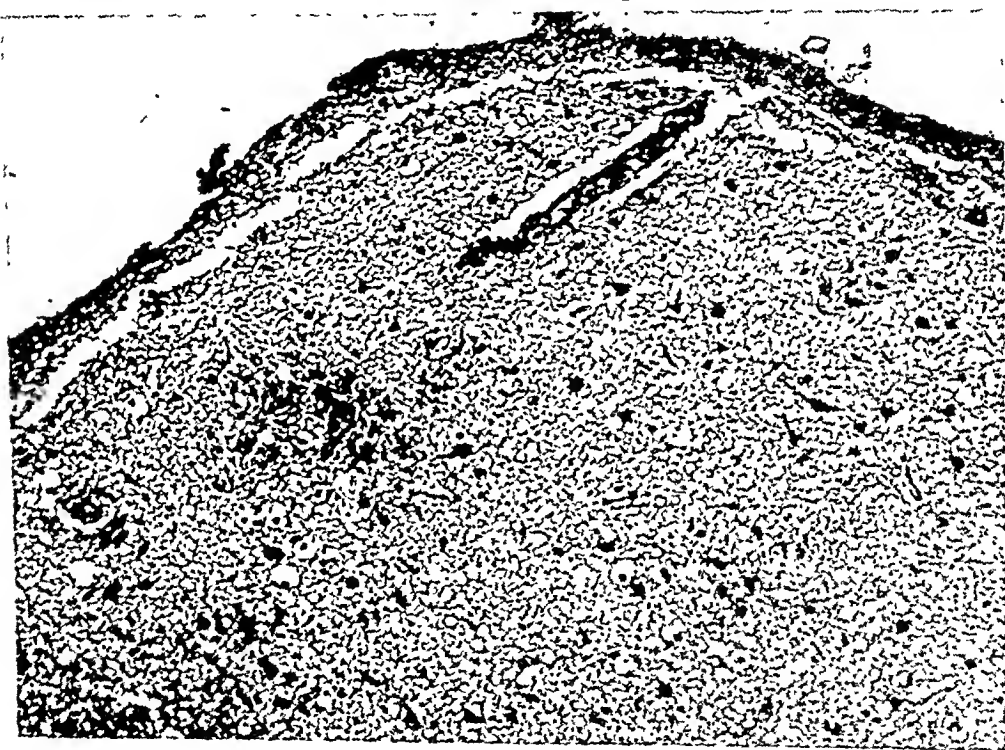


Fig 5.—Cerebral prefrontal cortex. ( $\times 200$  hematoxylin and eosin, see text.)

In anticipation of an encephalogram and in order to see how much air was still present in the subdural space, a recheck examination of the skull was done on Jan. 3, 1948. A large collection of subdural air was seen still present over the frontal area of the brain.

An encephalogram under local anesthesia was done on Jan. 7, 1948 (Dr. H. T. Wyeis). One hundred thirty c.c. of clear spinal fluid was removed and 120 c.c. of air injected. The spinal fluid showed 7 lymphocytes, protein was 26 mg. and the chlorides were 728 mg. The spinal fluid Wassermann and colloidal gold curve were negative.

*Roentgenogram Report.*—Excellent visualization of the ventricular system and the subarachnoid patterns was obtained by encephalography. The subarachnoid channels were prominent and there was some extra-arachnoid air





Fig 6 —Encephalograms A, anteroposterior, and B, lateral view, showing dilation of ventricles and increase in intergyral subarachnoid spaces Silver clip in right prefrontal cortex identifies site of biopsy

around the vertex. There was evidence of a moderate degree of communicating hydrocephalus. The third ventricle was quite large and it appeared to be partially divided by a septum which extended in a vertical direction from the floor to the roof. Conclusions: communicating hydrocephalus and brain atrophy of moderate degree. The silver clip in the right cerebral hemisphere (Fig. 6, A and B) should be noted.



Fig. 7.—Incision for direct exposure of sagittal sinus preliminary to Diotrast injection for sinography. Note large fontanelle and wide biparietal distance.

Since the infant's symptoms were noticed shortly after birth and there was no history of birth trauma, it was thought that the subdural hygroma and the increased subarachnoid channels over the surface of the brain might be due to an occlusion of the sagittal sinus in utero which prevented the normal absorption of the subarachnoid fluid through the arachnoid villae. Accordingly, on Jan. 16, 1948, an attempt was made to inject Diotrast into the sagittal sinus at the anterior fontanelle. No blood could be obtained after three insertions of the needle and it was decided to expose the sinus. This was done three days later. A 2½ cm. incision was made across the anterior fontanelle (Fig. 7). The scalp and the periosteum were dissected from the dura and the sagittal sinus exposed. A 20-gauge needle was inserted into the sinus. Blood was easily withdrawn and 10 c.c. of thirty-five per cent solution of Diotrast were injected rapidly. An x-ray exposure of the lateral view was made after 8 c.c. of this injection (Fig. 8 A). Another 8 c.c. were injected and an additional exposure was made for stereoscopy. The needle was removed and a larger 18-gauge needle inserted, followed by 8 c.c. of Diotrast and a final x-ray exposure in lateral view (Fig. 8 B). No anterior posterior projections were taken because an excessive amount of Diotrast had been used for the lateral views. The incision was then closed. There were no untoward effects from the injections.\*

The roentgenograms following the Diotrast injection were reported upon by Dr. Barton Young:

\*Diotrast sensitivity tests were negative before the injections.



Fig 8A—Diotrast sagittal sinogram showing obstruction of sinus just posterior to anterior fontanelle. Ten cubic centimeter of 35 per cent Diotrast rapidly injected through a 20-gauge needle. Note filling of anterior one-third of sinus and partial collateral venous filling.

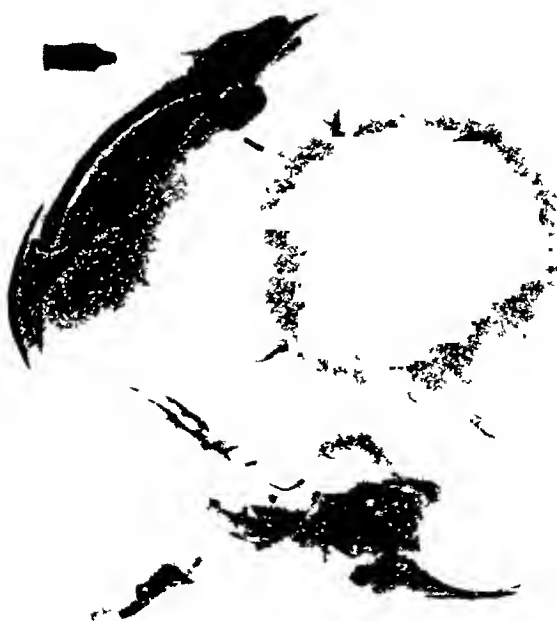


Fig 8B—Immediately after injection as shown in Fig 8A an 18-gauge needle was substituted for the 20-gauge needle and 8 cc of 35 per cent Diotrast injected. The obstruction is now more striking, the anterior one-third of the sinus is completely filled and the collateral circulation from the anterior one-third to the transverse lateral sinus is clearly demonstrated.

"The superior sagittal sinus apparently was blocked a short distance posteriorly to the anterior fontanelle. The Diotrast puddled in the fontanelle region and passed through the veins that communicate with the sinus anterior to the block instead of flowing posteriorly into the transverse sinus which normally drains the superior sagittal sinus. The anterior third of the sagittal sinus down to the crista galli was well visualized. A roentgenogram following the last injection with the 18-gauge needle showed collateral venous pathways from the anterior third of the sagittal sinus flowing in the direction of the transverse sinus. (Figs. 8A and 8B.) It was concluded that the cause of this block is not known but it is thought that we were dealing with a developmental anomaly or lack of development in this region.



Fig. 8C.—For a comparison, 8 c.c. of 35 per cent Diotrast was injected through a scalp incision across the anterior fontanelle into the sagittal sinus of another infant, who had a traumatic subdural hygroma. There was no motor weakness. Note the excellent filling of the sagittal sinus, torcular Herophili, and both lateral and sigmoid sinuses.

*Clinical Course.*—At the time of discharge from the hospital on Feb. 14, 1948, the neurological examination showed no change from that at admission except for slight improvement in muscle power.

#### DISCUSSION

Although only one case is presented and histologic evidence of the occlusion of the sagittal sinus is not available, it appears reasonable that the facts presented permit theoretical discussion.

In the fetus, occlusion of the sagittal sinus distal to the anterior third due to either congenital stenosis or thrombosis from any cause, could impair drainage of the important cortical veins supplying the paracentral lobule and inhibit

its development. Absence of adequate cerebral stimulation from this lobule to the anterior horn cells might in turn result in a decrease of or abnormal function of these cells, which would be reflected finally by the fetal stage of development of the muscles at birth.

It is well established that the lower extremities are more involved in amyotonia congenita than the upper. The paracentral lobules supply the lower extremities. The face and upper extremities may show less involvement in some cases because the cortical veins of these areas may drain by the vein of Labbe into the nonobstructed transverse sinns.

If occlusion of the sagittal sinus were a frequent cause for amyotonia congenita, one would expect corroboration in reported autopsies. However, attention on necropsy material has been centered on the spinal cord and the muscles, and the sagittal sinus has not been examined in most cases. As late as 1946 Freeman states, "The cortical changes in amyotonia congenita have attracted little notice."<sup>4</sup>

It is my belief that the subdural hygroma was an additional factor in producing the cerebral changes and the clinical picture. However, it plays a secondary role.\* It is recognized that a large portion of the subarachnoid fluid drains into the sagittal sinus via the arachnoid villi or paechionian bodies. If this pathway of absorption is blocked by occlusion of the sinus, it is entirely possible for the fluid to dam back from the paechionian villi into the subarachnoid and subdural space and produce a hygroma. Bailey and Hass have reported bloody subdural hygromas and hematomas following acute thrombosis of the superior longitudinal sinus in infants.<sup>5</sup> They believed that the hemorrhage into the subdural space was the result of the venous obstruction. All their patients had a period of normal postnatal development and none had symptoms of amyotonia congenita. The patient's ages were 3½ months, 10 months, and 6 years. However, one would not expect an occlusion of the sagittal sinus after birth as occurred in their patients to produce the same symptoms as that produced by an occlusion before birth. This conclusion is supported by the experimental work of Beck and Russell on thrombosis of the superior longitudinal sinus.<sup>6</sup> These investigators "found that in the dog and cat the greater part of the sinus could be suddenly obliterated without any obvious impairment of normal function. Reparative processes ending in organization and recanalization of the occluding material whether muscle or cotton wool, proved surprisingly effective." Beck even attempted these experiments on litters of puppies and kittens 6 to 8 weeks old. All the animals remained in perfect health up to the time of being killed with the exception of one puppy which died thirty-eight hours after operation from blood loss. The animals were sacrificed after a period of 5 to 7 weeks. In those in which a maximum of the sinus

\*Tuthill and Levy<sup>7</sup> report an infant with amyotonia congenita who showed the classical type of muscle biopsy and in whom weakness of the lower limbs was noted when 10 days of age. The condition became progressive, spread to the arms, and the infant died at 6 weeks of age. Although no mention is made of an examination of the sagittal sinus the finding on page 593 is interesting: "The skull measured 13.8 by 8.6 Cm. and was very thin. The brain was slightly hyperemic and rather edematous. The meninges were likewise edematous, particularly in the temporal lobe, the membranes of which appeared like cysts filled with clear fluid." The above authors apparently attached no significance to this finding but it certainly looks like subdural hygroma.

was occluded there developed fullness of the veins of the retina but no papilledema. In no case was there a thrombosis of any of the superficial cerebral veins. A variable but slight dilatation of the ventricles was found in puppies. Beck makes no mention of any abnormality in the amount of subarachnoid fluid or whether or not there were abnormal collections of subdural fluid. None of the animals showed any evidence of paralysis or motor weakness. It would thus appear that after birth in very young animals the collateral circulation apparently is adequate. That this might also be true to a certain extent in human infants is evident from the fact that in certain cases of amyotonia congenita the patient gradually recovers power in the extremities. It is the writer's belief that in the fetus the collateral circulation following occlusion of the sagittal sinus may be inadequate. However, there is no experimental proof for this statement.

The term sagittal sinus occlusion is used in the case report because it is not known why or how the sinus became obstructed. Caudal epidural anesthesia was used but no ill effects were reported. The infant's mother gave no history of any intercurrent infections while carrying the baby which might lead to a thrombosis or infection of the sinus of the fetus. She did give a history of falling and striking her buttocks when she was eight months pregnant and although she was slightly shocked there was no vaginal bleeding and there were no symptoms to suggest any hemorrhage into the uterus or fetus. A biopsy of the sinus was not done because this would jeopardize any chance the infant had for possible recovery.

#### CONCLUSIONS

1. The etiology of amyotonia congenita (Oppenheim's disease) is obscure.
2. Most reports stress the findings in the muscles and the spinal cord.
3. An almost complete absence of the large multipolar cells of Betz in the paracentral lobule has been reported in some cases of amyotonia congenita.
4. No theory has been advanced as to why these cerebral changes occur.
5. A case of amyotonia congenita is described associated with occlusion of the sagittal sinus and bilateral subdural hygroma.
6. It is suggested that occlusion of the sagittal sinus in the fetus produced a bilateral subdural hygroma by obstruction of the subarachnoid fluid drainage into the arachnoidal villi and also an obstruction of the venous drainage from the paracentral lobule into the sinus and resulted in the suppression of the normal development of the fetal cortex of this lobule which is parasagittal and innervates the lower extremities.
7. This failure of the fetal motor cortex to develop or function properly resulted in retarded development or function of the anterior horn cells and finally abnormal development of the muscles in the extremities.
8. It is, therefore, suggested that occlusion of the sagittal sinus in the human fetus might be one cause for the syndrome of amyotonia congenita.
9. Autopsies in these cases should include a search for subdural hygroma and a careful dissection and microscopic examination of the sagittal sinus and other dural sinuses and veins.
10. A method for visualizing the sagittal sinus with diotrast is described.

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## ERYTHEMA MULTIFORME EXUDATIVUM: STEVENS-JOHNSON SYNDROME

CARDIOVASCULAR AND CENTRAL NERVOUS SYSTEM INVOLVEMENT

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RENEWED interest has arisen in the syndrome of severe erythema multiforme, evidenced by many recent case reports<sup>1-56</sup> and several good reviews.<sup>1-7</sup> Most of the cases are reported under the names of erythema multiforme exudativum, erythema multiforme bullosum, or Stevens-Johnson disease. The clinical and laboratory picture is protean, but the criteria demanded by all are multiform skin and mucous membrane lesions, conjunctivitis, and constitutional symptoms compatible with an acute infectious disease. The skin lesions vary from a few scattered macules to extensive, hemorrhagic bullae. The mucous membranes of the mouth, pharynx, larynx, genitalia, and anus may be involved in varying degrees. Oral lesions are the most common and usually begin as small vesicles which become shallow ulcers, often covered by gray pseudo-membranes. The conjunctivitis varies from mild reaction to destruction of the eye. Systemic symptoms also vary markedly. The temperature may be normal or run a septic course for several weeks. There may be only photophobia and sore mouth, or there may be marked malaise and prostration. Many patients present signs of atypical pneumonia.<sup>6</sup> Most patients recover completely, but some remain blind,<sup>48-50</sup> and fatal cases<sup>2-10</sup> have been reported. The syndrome seems to be more severe in infants and children. The white cell count varies from leucopenia to marked leucocytosis, but there is usually an increase in neutrophils. Blood cultures are sterile, and extensive search for virus etiology has been negative.<sup>2, 4, 6, 26</sup> Drug reactions have been suggested as causative factors<sup>3, 7, 10-12, 38</sup> and the disorder occasionally follows vaccination.<sup>5, 46, 47</sup> Epidemics suggest an infectious origin.<sup>2, 27</sup> Many feel that the syndrome is a definite clinical entity. Other observers attempt to separate the cases with catarrhal conjunctivitis from those with purulent conjunctivitis, or to place those with bullous or macular lesions into different groups. Etiologic classification seems impossible.

This paper will record five cases, each interesting in itself, each fulfilling the criteria for erythema multiforme exudativum, but sufficiently different to arouse doubt as to all being the same clinical entity. They also suggest that the central nervous system and the heart may be involved more frequently than is generally suspected.

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CASE 1.—T. R., a 5-year-old white male child, was admitted on Nov. 19, 1947, to Babies and Childrens Hospital of Cleveland with complaints of cough, fever, and sore mouth. Family history and past history were irrelevant. Two weeks before admission he developed a hacking cough of progressive severity, and two days before admission, he developed an inspiratory stridor and a mild conjunctivitis. Temperature rose to 103° F., the cough became productive of tenacious sputum, bullous lesions developed in the mouth, and the patient became increasingly toxic. During the week before admission, he had been hospitalized elsewhere and had been treated with large dosages of penicillin, sulfadiazine, and streptomycin without obvious benefit.

On admission the patient was a well-developed and well-nourished boy, appearing acutely and seriously ill with temperature of 39.6, pulse 124, respiration 34, and blood pressure 90/60. Positive physical findings were limited to skin, mucous membranes, eyes, and lungs. There were a few scattered, raised, erythematous lesions on the trunk. Oral mucous membranes were covered with large vesicles. Conjunctivae were diffusely inflamed. From the eyes and nose drained a large amount of thick, purulent discharge. There was generalized lymphadenopathy but the spleen was not palpable. The heart was normal. There were a few râles at the bases of the lungs.

Repeated urinalyses were negative. Red cell count and hemoglobin were normal. White cell count on admission was 15,000 with 76 per cent neutrophils and 2 per cent eosinophils. This slowly returned to normal. Cold agglutination test was positive 1:1,024. Cultures of secretion from the eye grew *Staphylococcus aureus*. Nose and throat cultures showed predominance of fusiform bacillus. Bilateral, patchy, pulmonary infiltration was seen in roentgenogram of the chest.

For the first week the patient continued to appear toxic and seriously ill. The temperature spiked daily to 40° C. The skin lesions became more widespread, and then vesicular. The vesicles broke to form irislike lesions. The vesicles in the mouth broke down to form ulcers covered with dirty necrotic membrane. The boy was given penicillin in usual dosage and supported with parenteral fluids. By the eleventh hospital day all lesions had cleared markedly, he was afebrile, and was discharged.

*Comment.*—This case is typical of most of those reported. The conjunctivitis was purulent and cultures grew *Staph. aureus*. The oral mucous membranes were covered with the typical dirty white membrane. The skin lesions were multiform and some were vesicular. There was marked evidence of systemic infection but the patient was not precariously ill. White blood count was only moderately elevated but there was a marked shift to the left. There was evidence of pneumonia and cold agglutination test was strongly positive. Etiology could not be determined. Recovery was apparently complete.

CASE 2.—D. C., a 7-year-old white girl, was admitted on Jan. 4, 1948, from another hospital with a diagnosis of meningitis. Signs of inflammatory reaction were still present in the spinal fluid, possibly as result of treatment; cerebral spinal fluid cultures were sterile and an etiologic diagnosis was not made. The details of this illness may not be pertinent except that she had been treated with penicillin, streptomycin, and sulfadiazine. On the eighteenth hospital day she was considered well and ready for discharge when she broke out with a generalized, papular rash. This became very marked, even covered the palms and soles, and rapidly developed into small vesicles. Within fourteen hours temperature had risen to 40° C, she was extremely toxic, the oral mucous membranes were involved with numerous small vesicles, and a marked conjunctivitis developed. White blood count was 15,400 with 90 per cent neutrophils. Lumbar puncture was negative. The patient had been vaccinated one year previously. She had never had varicella. Because of the resemblance of her condition to varicella and the presence of an epidemic in the community, she was transferred to the contagious division of City Hospital.

At City Hospital her condition was thought to be varicella and she was placed in the varicella ward. For the next seven days she was seriously ill. The vesicles formed pustules, dried on the fifth day, and fell off on the tenth day. New lesions appeared and there were various stages at the same time. The vesicles in the mouth coalesced, ruptured, and formed ulcerations that were covered by a thick, extensive, gray-white membrane. She complained bitterly of a sore mouth and refused to swallow. There was a marked purulent conjunctivitis. Temperature spiked to 39° C. daily for seven days and then gradually fell to normal. Oral mucous membranes and eyes began to improve about the seventh day and had cleared markedly by the tenth day. Examination of chest was normal throughout. White cell count rose to 23,000 with 88 per cent neutrophils but fell to normal before discharge. Lumbar puncture was negative. Blood cultures were negative. Cultures from eye grew *Staph. aureus*. She was treated with penicillin and sulfadiazine systemically, and boric acid washes and sulfonamide ointment were used locally to eyes.

By the fifteenth hospital day she seemed to have recovered completely but on the seventeenth day she developed a typical case of varicella that ran a normal course.

*Comment.*—This case is similar to Case 1. It illustrates the difficulty that one may have in diagnosis.<sup>5</sup> It is also "typical" of most of the case reports in that the peripheral involvement paralleled systemic symptoms.

CASE 3.—G. K., a one-year-old Greek male infant, was admitted on April 16, 1948, with complaints of fever, rash, sore mouth, and conjunctivitis. Past history was negative except for eczema. He had received a smallpox vaccination on April 8, 1948, and six days later developed a generalized rash. The next day fever, restlessness, conjunctivitis, and a sore mouth developed, and when these symptoms progressed, hospitalization was recommended.

Admission physical examination revealed a well-developed, well-nourished infant who appeared acutely and seriously ill. Temperature 39° C., pulse 165, respiration 40, blood pressure 100/70. He was listless when left alone and extremely irritable when disturbed. There was a generalized, confluent, irregular, patchy erythema with raised edges, most marked over the extensor surfaces of the extremities. Lymph nodes were generally enlarged. Eyelids were swollen and conjunctivae were markedly inflamed but there was no discharge. Mucous membranes were fiery red and there were a few ulcerations covered with a gray exudate. There were fine rales at the bases of the lungs. Heart rate was fast but tones were of good quality. Neck was stiff.

Urinalyses were negative except for a few hyaline casts. Red blood count and hemoglobin were normal. White blood count varied between 20,000 and 35,000 and there was at each examination a marked increase in neutrophils. White blood count was normal on discharge. Blood cultures and routine agglutinations were negative. Cold agglutinations were positive 1:128. The spinal fluid contained 20 lymphocytes per cubic millimeter but sugar, protein, and chlorides were normal. Cultures from throat and eyes grew several common organisms. Roentgenogram of the chest was normal. Electrocardiogram showed sinus tachycardia and marked increase in P-R interval. These findings persisted on discharge.

For the first week the patient continued to have high spiking temperatures. He was very toxic, extremities were tremulous, and he assumed the position of opisthotonos. The heart rate remained rapid and occasionally there was a gallop rhythm. Penicillin, supportive parenteral fluids, and boric acid eye washes were used in treatment. Many fine vesicles developed over the skin lesions, coalesced, ruptured, and formed a thick scab that could easily be peeled off. Improvement was gradual but marked, and he was discharged on the seventeenth hospital day entirely well except for slight pigmentation and the persistent electrocardiographic changes.

*Comment.*—Erythema multiforme following vaccination is rare.<sup>46-47</sup> As in this case, it is more common with a past history of eczema.<sup>46</sup> This patient's conjunctivitis and oral lesions were not very severe. Skin involvement was extensive but not serious. Systemic symptoms, however, were very severe, and

during the first few days prognosis remained guarded. The listlessness and irritability, the meningeal signs, and the opisthotonos suggested central nervous system involvement, confirmed by pleocytosis in the spinal fluid. Vaccinia encephalitis received consideration but its rarity and the benign course here made it appear unlikely. The electrocardiographic changes are interesting, and the cardiac involvement was suggested clinically, but the significance is not understood.

CASE 4.—E. M., a 12-year-old white girl, was admitted on Feb. 5, 1948, with complaints of fever, delirium, and adenitis. Past history and family history were noncontributory. Five days before admission the patient developed a sore throat followed by a mild temperature elevation and a swelling under the left ear. The next day her temperature rose to 105° F., and she became toxic and delirious. The conjunctivae became inflamed, she began to vomit frequently, and the mass in the neck became larger. She complained bitterly of a sore mouth. Sulfadiazine was begun by the private physician but this was vomited and penicillin in beeswax was resorted to without obvious benefit. The acute symptoms persisted and she was admitted to another hospital. Physical examination there revealed temperature of 105° F., delirium, a hard, egg-shaped mass at the angle of the jaw, conjunctivitis, stomatitis, and a scanty macular rash over the trunk. She was treated with penicillin, streptomycin, and parenteral fluids. The mass in the neck subsided promptly but she remained seriously ill and was referred to the Babies and Childrens Hospital.

Admission physical examination revealed a large, obese girl who was delirious and appeared acutely and seriously ill. Temperature was 40.3 C., pulse 120, respiration 70, and blood pressure 105/70. A scanty, pink, macular eruption that blanched on pressure was spread over the entire body, including the palms and soles. On the left side of the neck extending behind the ear there was a mildly swollen, ecchymotic, hard, poorly localized area 6 by 4 cm. The eyelids were ecchymotic, the conjunctivae were markedly inflamed, but there was no discharge. Oral mucous membranes were inflamed and edematous but there were no ulcerations or exudate. The heart rate was fast and tones were of poor quality. There were frequent fine râles at both bases.

Admission urinalysis showed a trace of albumin and many leucocytes, and 10 to 12 leucocytes per high power field in uncentrifuged specimens persisted until discharge. There was a transient microscopic hematuria on the eighth day. During the first week the white blood count remained around 20,000 with over 80 per cent neutrophils and a marked shift to the left. The count dropped slowly to normal before discharge. There was a slight hypochromic anemia. Spinal fluid was normal. Agglutinations for typhoid, paratyphoid, dysentery, rickettsia, tularemia, and brucellosis were negative on several occasions. Repeated blood, spinal fluid, urine, and stool cultures on various types of media were negative. Intracerebral and intraperitoneal injections of blood and spinal fluid into guinea pigs and mice were negative. Cold agglutinin titer was 1:64, rose to 1:128, and then fell again to 1:64. Heterophile titer remained 1:64. No atypical lymphocytes were seen. Cephalin flocculation was +4. Serum drawn on the sixteenth hospital day was reported by Dr. Isaac Ruchmann of Cincinnati Children's Hospital to give positive complement-fixation titer for toxoplasmosis. For the first few days her temperature spiked to 40° C. daily, then slowly fell to normal. During the febrile period the child was toxic, delirious, and seemed precariously ill. The respiratory rate remained around 80 and occasionally a gallop cardiac rhythm was heard. Râles persisted. She complained of a sore mouth and of photophobia and vomited almost everything offered her. Serum chlorides fell to 84 meq. and serum potassium to 2.8 meq. Parenteral fluids served to maintain hydration and slowly brought the electrolytes back to normal. With hydration, blood pressure rose to 150/90, but nonprotein nitrogen was normal. Roentgenogram of chest revealed accentuation of pulmonary hilar markings; inversion of T waves and a prolonged Q-T interval were seen in the electrocardiogram. Malaise and anorexia persisted even when her temperature became normal. Skin, eyes, and mucous membrane lesions cleared within one week. Some of the skin macules left residual pigmentation. There was

never any discharge from eyes, nor any vesicular formation on skin or mucous membranes. Blood pressure remained around 150/90 for two weeks but fell to 130/70 shortly before discharge. Tachycardia persisted and discharge electrocardiogram on the twentieth day still showed abnormal T waves.

*Comment.*—One might question the diagnosis of erythema multiforme in this case, yet criteria for this diagnosis were present. The systemic symptoms were out of proportion to the eye, mucous membrane, and skin involvement, and there were no bullous or exudative lesions.

The clinical picture somewhat resembled acute toxoplasmosis<sup>62</sup> but the high white blood count, the complete recovery, and the negative spinal fluid make that diagnosis unlikely despite the positive complement fixation test. The value of the complement fixation titer in acute toxoplasmosis is apparently not too well substantiated.<sup>62-66</sup> The positive heterophile reaction may have been non-specific, even though the clinical picture was compatible with infectious mononucleosis. The lymphocyte count was always low and no atypical cells were seen.

The abnormal electrocardiogram was felt to be due to myocarditis or possibly to low serum potassium. Clinical condition suggested myocarditis and the finding persisted even after the potassium returned to normal. The significance of the hypertension was not known but it might be important in view of the pathologic findings in the next case. The degree of hypopotassemia resulting from the vomiting is also interesting. Our impression had been that lower levels often result from vomiting than from diarrhea.

CASE 5.—V. S., a 9 month old white female infant, was admitted on March 16, 1948, for transfusion following hemorrhage from an incised cervical lymph node. Past history was irrelevant except for a mild inspiratory stridor noted when the patient was excited, present for several months. The present illness had begun five days before admission with fever, pharyngitis, vomiting, and an enlarged cervical node. Sulfadiazine was vomited and penicillin in oil did not seem to help. The symptoms persisted, the node enlarged, and was incised the day before admission. It drained a thin, bloody material, and during the next twenty four hours the patient became very pale, and hospitalization was suggested.

On admission the patient was a well developed, well nourished, pale infant who appeared acutely and seriously ill. She was extremely irritable when disturbed but listless when left alone. Temperature was 40° C., pulse 200, respiration 70. There was a small mass at the angle of the left jaw draining a thin, bloody material. Skin and mucous membranes were normal. Heart rate was fast and tones were of poor quality. The lungs were clear and the rest of the physical examination was negative. Admission hemoglobin was 6 gm. with 2.1 million red blood count. Following transfusion the hemoglobin rose to 65 per cent. White blood count on admission was 14,000 with 65 per cent neutrophils and after the transfusion was 23,000 with 70 per cent neutrophils. White blood count was normal by the eighteenth day. Catheterized urine showed traces of albumin and many epithelial cells. Several blood and urine cultures were negative. Routine agglutinations were negative. Spinal fluid showed from 15 to 18 lymphocytes on several occasions. Chemical determinations on spinal fluid were normal.

The patient received penicillin and sulfadiazine and was given several transfusions. Temperature spiked to 39 to 40° C. for the first fourteen hospital days and the infant remained acutely and seriously ill. She was irritable, refused most feedings, and required supportive parenteral fluids. Respiratory rate remained rapid, and heart tones were of poor quality. Within twelve hours after admission she developed a scanty, papular rash over the trunk that spread rapidly to involve the extremities. Conjunctivae became inflamed and lids

became edematous, but there was no discharge. Oral mucous membranes became red, denuded, and seemed very painful. On the second day the vagina and urethra became inflamed. The skin was normal by the third hospital day and the eye and mucous membrane lesions cleared by the tenth day. The mass in the neck subsided quickly. Roentgenogram showed only prominent lung markings. Improvement was gradual and even after the temperature returned to normal she was very irritable and her pulse rate was rapid. Late in the illness her pre-existing stridor became more marked. She was to be discharged on the twenty-second day but was laryngoscoped first to ascertain the cause of the stridor. The larynx was easily seen and seemed normal, but as the laryngoscope was withdrawn, there was apparently cardiac standstill and the infant died suddenly.

On autopsy aneurysms of the coronary arteries were found. One of these had ruptured, giving a hemopericardium. The microscopic picture was that of periarteritis nodosum. The other tissues were normal. This case will be reported in more detail elsewhere.<sup>67</sup>

*Comment.*—As in Case 4 the systemic symptoms overshadowed the involvement of the eyes, mucous membranes, and skin. Again a diagnosis of erythema multiforme could be questioned, but the criteria were fulfilled and no other diagnosis could be substantiated. The relationship to periarteritis<sup>57-60</sup> is not known, but a strikingly similar case<sup>58</sup> is reported that makes coincidence unlikely. It has been hypothesized that both could be caused by a virus and both can apparently be produced by sensitization to sulfonamide.<sup>10-12, 61</sup> The extreme irritability and the pleocytosis of the spinal fluid is similar to Case 3.

#### DISCUSSION

Cases 4 and 5 had no lesions that could be called exudative or bullous and systemic symptoms were out of proportion to the eye, skin, and mucous membrane involvement. In Cases 1 and 2 the systemic symptoms seemed to parallel the other findings but in Case 3 the skin involvement was out of proportion to the eye and mucous membrane involvement. This is true of the reported cases in which varying degrees and combinations of the signs and symptoms occurred. However, they all fulfill the criteria mentioned above. Formerly the group of cases included in this syndrome was even larger in that Osler's erythemas and other conditions were included, many of which were found to be lupus erythematosus or Schönlein-Henoch purpura.<sup>7</sup> We have no suggestion as to terminology or classification but feel that several clinical and etiologic entities may be eventually separated from this interesting group of cases.

Electrocardiograms were performed in two patients and both showed abnormalities. A third case at necropsy had aneurysms of the coronary arteries. These findings suggest that cardiac and vascular involvement is more frequent than generally suspected. Keil<sup>2</sup> stated, however, that the electrocardiogram was not significantly altered, and only two other cases<sup>46, 56</sup> were found with abnormal tracings. The abnormalities in our cases may have been nonspecific, but it would be interesting if more careful cardiac evaluations could be made. Marked fragmentation and degeneration at the myocardium may be found at autopsy.<sup>3, 5</sup>

Central nervous system involvement is often suggested by the irritability and the delirium but there is little supportive laboratory evidence. Two of the four patients in whom the spinal fluid was examined had slight pleocytosis. Records of spinal fluid examinations were found in six reported cases<sup>7-9, 52-54</sup>

and five of these were normal, the other showed 24 lymphocytes. Post-mortem examinations of the brain have revealed little more than edema and congestion.<sup>6, 10</sup>

## SUMMARY

1. Five cases that fulfill the criteria of severe erythema multiforme are reported.

2. Brief consideration is given to the variability of the picture and the possibility of the syndrome being a clinical entity.

3. Cardiovascular involvement as well as signs of central nervous system disturbance were present in severe cases. Literature on these phases is reviewed.

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## THE DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER AND INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

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RHEUMATIC fever, while classically manifested by fever, arthritis, and carditis, frequently appears with none of the major manifestations present, or with those manifestations overlooked or misinterpreted.<sup>1</sup> Surprisingly often rheumatic fever is diagnosed erroneously as an infection of the central nervous system, and less frequently the reverse error is made. It is the purpose of this paper to record several instances wherein rheumatic fever was considered to be poliomyelitis or meningitis, and to report two cases where meningococcus infections were misdiagnosed as rheumatic fever.

Fever, stiffness of the neck, headache, stiffness of the back, positive Kernig's maneuver, and abnormalities of the sensorium are generally considered cardinal signs of such infections of the central nervous system as poliomyelitis or meningitis. In addition, muscular weakness, especially in association with the signs of meningeal irritation, is strongly suggestive of acute anterior poliomyelitis. The presence of one or more of these manifestations during the course of rheumatic fever frequently leads to diagnostic error. Conversely, arthritis, purpuric rashes, and myocarditis all may occur in meningococcus infections and thereby mimic rheumatic fever.

That rheumatic fever may occasionally present signs suggestive of meningeal irritation has been commented upon in the past. Mention was made of the necessity of differentiation of acute rheumatic fever from poliomyelitis by Cheadle<sup>2</sup> in 1908 and by McCrae<sup>3</sup> in 1925. Rosenberg<sup>4</sup> noted the occurrences of stiffness of the neck in five patients in a series of 1,000 cases of rheumatic fever. Hansen<sup>5</sup> states that four patients with rheumatic fever were among a group of 271 patients referred to the University of Minnesota Hospitals with a diagnosis of poliomyelitis, and mentions the occasional reverse diagnostic error. According to Top,<sup>6</sup> of 843 patients referred to the Herman Kiefer Hospital as having poliomyelitis, twenty-one, or 2.5 per cent, were eventually determined to have rheumatic fever. Similarly, at the same hospital, of 2,269 patients referred with the diagnosis of meningococcus meningitis, six, or 0.26 per cent, were finally diagnosed as suffering from rheumatic fever. In our own wards the same situation prevailed, and the mistake was most common during epidemics of either poliomyelitis or meningitis. Rarely rheumatic fever may actually involve the central nervous system to the extent of producing restlessness, delirium, psychoses, convulsions, coma, or death, usually associated with hyperpyrexia—

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the so-called "cerebral rheumatism." Even more rarely, sterile meningitis manifested by the signs of meningeal irritation and spinal fluid pleocytosis may occur in the course of rheumatic fever.<sup>8</sup> In our cases, frank evidence of true involvement of the nervous system was lacking. Although the necessity for differentiation of rheumatic fever from infections of the central nervous system has long been known and the correct diagnosis usually is easily reached, it is apparent that this problem is not widely appreciated.

#### CASE REPORTS

CASE 1.—D. K. was a 16-year-old white boy. This patient entered the hospital complaining of "paralysis of the legs" for three days. Five weeks previously he had suffered from a "cold" with sore throat and stiffness of the neck, and had been treated with sulfonamides. He recovered in three days and was able to return to work.

Three days preceding admission he noted general muscular stiffness and such extreme pain in his extremities that he was unable to move at all. The next day he was able to move his arms but his legs remained "paralyzed." He noted some pain in the hip joints. He was taken to another hospital by automobile, and, while attempting to walk, he collapsed. He was referred to the Isolation Division with a diagnosis of poliomyelitis.

Past history revealed that the patient had frequent colds, and had suffered from scarlet fever at the age of 3 years and measles at the age of 11 years. He denied having had rheumatic fever.

*Physical Examination.*—Temperature was 102° F., pulse 90, respiration 22. The patient was a well-developed and well-nourished young man who appeared moderately ill and was unable to move his legs. A faint macular rash was noted over the anterior axillary area and the upper arms. The inguinal nodes were enlarged but nontender. The teeth were carious. The throat was slightly red-dened. The neck and back were moderately stiff on forward flexion. The lungs and heart were normal, as was the abdomen. Local tenderness was noted over the right sacroiliac joint. Apparent weakness of flexion and adduction of the thighs was present. Spasm was noted in the hamstring and gluteus maximus muscles. Sensation was intact. The reflexes were normal.

*Laboratory Examination.*—Hemoglobin was 85 per cent; red blood cells 4.5 million per cubic millimeter; white blood cells 12,200 per cubic millimeter; neutrophils 86 per cent; lymphocytes 12 per cent, monocytes 2 per cent. Urinalysis was negative except for the slightest possible trace of albumin. Sedimentation rate was 50 mm. per hour, Wintrobe (corrected).

Lumbar puncture revealed a clear fluid under normal pressure. This fluid contained 5 lymphocytes per cubic millimeter. Total protein content was 69.1 mg. per cent, glucose was 85 mg. per cent. The Lange gold curve was normal. Culture was negative.

*Course.*—On the day following admission to the hospital, both wrist joints became swollen and tender. Motion of the hip joints was definitely painful, and this appeared to be the reason for the patient's inability to move his legs. A soft, systolic murmur appeared at the apex. An electrocardiogram revealed flat T waves in Leads T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>. The P-R interval was 0.16 second. Following the administration of sodium salicylate the joint manifestations and fever subsided, although the murmur persisted. The patient was taken from the hospital by his parents against advice on the sixteenth hospital day.

*Comment.*—In this patient presumably the apparent muscular weakness was really unwillingness to move his lower extremities because of pain. The

deep reflexes in the extremities remained normal, however. The diagnosis became apparent quickly upon the development of frank rheumatic arthritis, a systolic murmur, and electrocardiographic abnormality. The elevated spinal fluid protein content was unique in our experience.

**CASE 2.**—(C. O. B. was a 17-year-old white boy. This patient was en route from Farragut, Idaho, to San Francisco when, during the night of July 24, 1943, he complained of severe headache, stiff neck, and slight fever. He was taken off the train, hospitalized, and observed for the possibility of meningitis. Spinal fluid examination was negative. It was observed, however, that his knees were slightly painful and swollen; it was also elicited that three days previously his right ankle had become painful and swollen for a day, which condition he had attributed to an injury. A month previously he had had a febrile upper respiratory infection, but had convalesced rapidly. He had had no previous rheumatic manifestations. The headache and stiff neck subsided in two days and the swelling in his knee largely disappeared. He was then transferred to the Naval Hospital, Oakland.

On admission, Aug. 1, 1943, he was afebrile and complained only of fatigue and slight pain in the left knee. Examination was negative except for slight tenderness on extreme range of motion and moderate apical systolic murmur over the heart with a sinus tachycardia of 100 per minute. His blood pressure was 106/58. His laboratory data revealed a normal urine and blood count. The blood sedimentation rate was 23 mm. and the electrocardiogram showed a partial heart block with a P-R interval of 0.24 second.

**Course.**—The patient rapidly improved on routine treatment with salicylates so that in four days his joint pains had disappeared. He was afebrile throughout his course and after six days his blood sedimentation rate was 10 mm. and the P-R interval 0.17 second. In six weeks the sedimentation rate had dropped to 5 mm.

**Comment.**—The occurrence of stiff neck and headache had led to the erroneous suspicion of central nervous system infection in this patient. The situation was clarified by the demonstration of pain on motion in the knee and of partial heart block.

**CASE 3.**—A. S., aged 17 years, male, was admitted to the Naval Hospital, Oakland, on Aug. 1, 1944, complaining of stiffness of the neck, weakness, and feverishness. A tentative diagnosis of meningitis was made and the patient transferred to the infections disease service. Examination there was entirely negative except for drowsiness, a slightly positive Kernig sign, and a somewhat stiff neck. The urine and blood Kahn reaction were negative. The white blood cell count was 20,350. Spinal fluid examination revealed a normal pressure, a total protein of 10 mg. per cent, sugar 66 mg. per cent, a negative colloidal gold curve and Kahn reaction, a cell count of 3, and a negative spinal fluid culture. Blood culture was negative. The throat culture was positive for *Staphylococcus aureus*. The patient was placed on sulfadiazine with no improvement after six days of therapy. At that time agglutination tests were done and were negative, as were the roentgenologic examination of the chest and a plain film of the abdomen. The blood sedimentation rate was 30 mm.

On August 9, when seen for the first time by one of the authors, it was elicited that he had had a febrile pharyngitis in mid-July, 1944, and that for several days prior to the onset of stiffness of the neck he had had aching pains in the back and knees which had continued to the present, but were mild and not associated with gross changes in the joints. An electrocardiogram was then taken and revealed a low  $T_1$  and  $T_2$  and diphasic  $T_3$ . His white blood cell

count at this time was 10,880 and the blood sedimentation rate was 31 mm. He was placed on full doses of salicylates and by August 15 he was afebrile, had no more joint pains, and was much improved. His blood sedimentation rate was still 31 mm. but dropped to 22 mm. by August 18 and to 14 mm. by August 21. His electrocardiogram at that time showed a normal  $T_1$  and  $T_2$ ;  $T_1$  was upright but low.

*Comment.*—This case illustrates that manifestations of the central nervous system may dominate the clinical picture and only when joint symptoms and evidences of carditis are specifically sought for will the diagnosis be clear. In this case the joint manifestations were very slight and led to further study only after sulfadiazine was ineffective and spinal fluid studies were negative.

*CASE 4.*—E. R. was a boy aged 13 years. Three days before entry, after seeing a moving picture, the patient felt chilly and noted pains in the low back. He felt better on the following two days but the night before admission noted a pain in the left leg which progressed from the ankle to the calf to the thigh. The pain was described as "severe and deep." Temperature taken a few hours before entry to the hospital was 99° F. Nausea and vomiting occurred a few hours preceding hospitalization. The patient was admitted to the Isolation Division with the diagnosis of possible poliomyelitis.

Past history was irrelevant except that the patient had had measles, mumps, and whooping cough. He had had a tonsillectomy in 1941. Family history was negative.

*Physical Examination.*—Temperature was 102° F., pulse 106, respiration 28, blood pressure 120/70.

The patient appeared to be in no acute distress. Slightly enlarged, non-tender, inguinal nodes were noted. A mucopurulent postnasal discharge was observed. The inferior turbinates were swollen. The neck was not stiff. The lungs were clear. The heart was normal in size, P-2 was greater than A-2. No murmurs were heard. Spasm of the left psoas and quadriceps was noted on extension of the hip and flexion of the knees, respectively. Forward flexion of the back was slightly limited. Reflexes were equal and hypoactive. Motor power and sensation were normal.

*Laboratory Examination.*—Hemoglobin was 14 Gm. per cent; red blood cells 4,900,000 per cubic millimeter; white blood cells 11,900 per cubic millimeter; neutrophils 76 per cent; eosinophils 1 per cent; basophils 1 per cent; lymphocytes 19 per cent; monocytes 3 per cent. Sedimentation rate, Wintrobe (corrected) was 46 mm. Urinalysis was negative except for 2 plus acetone. An electrocardiogram taken March 24, 1945, showed sinus tachycardia with partial A-V block. The P-R interval was 0.22 second with a cardiac rate of 106.

*Course.*—On the day following entry a presystolic gallop rhythm was noted at the apex. The left knee joint was swollen, very tender, and contained fluid. The following day his left wrist became similarly involved. The joint symptoms subsided promptly following the administration of sodium salicylate. Low-grade fever persisted for one and one-half months. Prolonged auriculo-ventricular conduction was noted on serial electrocardiograms over a period of five months. The sedimentation rate became normal in six months and the patient was discharged one month later.

*Comment.*—Suspicion of poliomyelitis was aroused by the occurrence of back pain and stiffness as well as muscle spasm in the right leg. The appearance subsequently of obvious arthritis and electrocardiographic abnormality in the presence of an extremely accelerated sedimentation rate served to establish the correct diagnosis.

CASE 5.—C. K. was a girl aged 9½ years. Four days before hospital entry, the patient had a mild sore throat. At that time she noted aching pain behind the right knee. On the day of entry she also noted pain in the right foot and toes and she became febrile. The patient was unable to bear weight on the right leg. She had had two episodes of epistaxis during the previous week. She entered the Isolation Division with a referral diagnosis of poliomyelitis.

Family history was negative. Past history revealed that the child had been well except for measles, mumps, and otitis media early in childhood.

*Physical Examination.*—Temperature was 100.2° F., pulse 90, respiration 20. Slightly enlarged, nontender, inguinal nodes were noted. There was slight injection of the anterior tonsillar pillars. The neck was slightly stiff on forward flexion. The heart, lungs, and abdomen were negative. There was slight limitation of forward flexion of the back. Straight leg-raising was limited to 70 degrees bilaterally. The area over the right metatarsophalangeal joints was hot and tender to palpation. No erythema or swelling were noted. Active dorsiflexion of the right foot against resistance was apparently weak and produced pain. Flexion of the thigh was weaker on the right than on the left. Reflexes were equal and active. Sensation was normal.

*Laboratory Examination.*—Hemoglobin was 13 Gm. per cent; red blood cells 4,700,000 per cubic millimeter; white blood cells 9,300 per cubic millimeter; neutrophils 54 per cent; lymphocytes 46 per cent; monocytes 2 per cent. Sedimentation rate, Wintrobe (corrected) was 22 mm. per hour. Mazzini and Kolmer were negative. X-rays of the right foot were normal. Lumbar puncture: Pressure 180 mm. of water, 4 cells, glucose 50 mg. per cent, Pandy negative, culture sterile.

*Course.*—The following day the right ankle joint was strikingly tender and swollen. The patient was transferred to another hospital with a diagnosis of acute rheumatic fever. The subsequent course was that of rheumatic fever.

*Comment.*—The presence of neck and back stiffness, hamstring spasm, and apparent weakness of dorsiflexion of the foot caused suspicion of poliomyelitis. The reflexes remained normal, however. The advent of frank arthritis and the absence of spinal fluid abnormalities were of diagnostic aid.

CASE 6.—J. S., was a girl aged 6 years. The patient had been diagnosed as having mild scarlet fever on April 19. On April 27 she developed headache and slight fever. On the next day her fever rose to 106.5° F. and she was hospitalized at another hospital where measles was diagnosed, although the white blood count was 16,000 per cubic millimeter. She was given 50,000 units of penicillin every three hours because some complication was suspected, and was referred to the Isolation Division.

Family history was irrelevant. The patient's past history was negative except for the occurrence of mumps at the age of 3 years.

*Physical Examination.*—Temperature was 105° F., pulse 110, respiration 25. Over the entire body, less dense on the extremities than on the face and trunk, were slightly raised, discrete, pink papules 0.5 to 1.0 cm. in diameter. Dried blood was noted in the right nostril. The gums were spongy and bled easily. There were very small white ulcers on the gums and buccal mucosa. The tonsils were enlarged and reddened, but no exudate was present. The neck was slightly stiff and pain was produced on forward flexion. The lungs were clear. The heart was not enlarged. A short systolic murmur was heard over the entire precordium. The abdomen was normal. The back was limited in forward flexion. Kernig's sign was questionably positive bilaterally. The extremities were normal. The reflexes were equal and active. Motor power and sensation were unimpaired.

*Laboratory Findings.*—Hemoglobin 92 per cent; red blood cells 4.6 million per cubic millimeter; white blood cells 11,050 per cubic millimeter. Urinalysis: albumin 1 plus acetone trace, 8 to 10 granular casts, 50 white blood cells, 1 to 3 red blood cells per high dry field. Sedimentation rate was 47 mm. per hour, Wintrobe (corrected). Cerebrospinal fluid: normal pressure, 4 red blood cells per cubic millimeter, glucose 50 mg. per cent, Pandy negative, protein 25 mg. per cent, culture negative. An electrocardiogram taken May 14 revealed the P-R interval to be at the upper limits of normal for this age and rate. It was 0.16 second with a cardiac rate of 95 per minute.

*Course.*—The rash faded over a period of four days. Salicylates were administered. No new joint symptoms developed, but the systolic murmur at the apex became louder and more prolonged and was transmitted to the left axilla. Low-grade fever persisted for twenty days. The sedimentation rate became normal on May 11. The patient was discharged to bed care at home on May 21. One month later the patient's private physician reported that the sedimentation rate remained normal, but that a loud systolic murmur was still present.

*Comment.*—The occurrence of the signs of meningeal irritation associated with a rash led to a tentative diagnosis of meningococcus infection. The proper diagnosis was established by the subsequent appearance and persistence of a prolonged, widely transmitted, cardiac murmur after the subsidence of fever in the absence of a positive blood culture or abnormal spinal fluid.

CASE 7.—C. M. was aged 5 years, a white male child. On the day preceding hospital admission the patient complained of pain in his legs. That evening he had a short, shaking chill followed by fever. His parents brought him to the hospital.

Past history revealed that the patient had had pertussis at the age of 6 months, a mild head injury at the age of 3½ years, and measles at the age of 4 years.

*Physical Examination.*—Temperature was 102.8° F., pulse 98, respiration 25. The child was irritable but did not appear ill. The pharynx was somewhat injected and slight submandibular adenopathy was noted. The neck was slightly stiff. Examination of the lungs, heart, and abdomen was negative. The back was stiff on forward flexion and the patient tended to sit in the tripod position. Straight leg-raising was limited bilaterally and Brudzinski's neck sign was positive.

*Laboratory Examination.*—Hemoglobin was 73 per cent; red blood cells 3.84 million per cubic millimeter; white blood cells 11,900 per cubic millimeter; polymorphonuclears 80 per cent; lymphocytes 20 per cent; sedimentation rate, Wintrobe (corrected) was 23 mm. per hour. Urinalysis was negative. Lumbar puncture was entirely normal. The patient was considered to have acute rheumatic fever. Two blood cultures taken on the evening of admission were subsequently reported positive for *Neisseria meningitidis*, Type I.

*Course.*—On the evening of admission the patient developed erythematous macules and papules over the extremities and abdomen. Tenderness was noted over both ankles, and painful swelling of the metacarpophalangeal joints of the first two fingers of each hand appeared. The patient became afebrile on the second day. No further skin or joint involvement occurred. A third blood culture taken on the fifth day was negative. The patient was given Sulfamerazine for two days before discharge on February 16.

*Comment.*—This patient presented a history of pain in his extremities without frank joint manifestations. The skin eruption was thought to be erythema multiforme. In the presence of a normal spinal fluid, central nervous system infection seemed excluded. The diagnosis was established only on the

CASE 5.—C. K. was a girl aged  $9\frac{1}{2}$  years. Four days before hospital entry, the patient had a mild sore throat. At that time she noted aching pain behind the right knee. On the day of entry she also noted pain in the right foot and toes and she became febrile. The patient was unable to bear weight on the right leg. She had had two episodes of epistaxis during the previous week. She entered the Isolation Division with a referral diagnosis of poliomyelitis.

Family history was negative. Past history revealed that the child had been well except for measles, mumps, and otitis media early in childhood.

*Physical Examination.*—Temperature was  $100.2^{\circ}$  F., pulse 90, respiration 20. Slightly enlarged, nontender, inguinal nodes were noted. There was slight injection of the anterior tonsillar pillars. The neck was slightly stiff on forward flexion. The heart, lungs, and abdomen were negative. There was slight limitation of forward flexion of the back. Straight leg-raising was limited to 70 degrees bilaterally. The area over the right metatarsophalangeal joints was hot and tender to palpation. No erythema or swelling were noted. Active dorsiflexion of the right foot against resistance was apparently weak and produced pain. Flexion of the thigh was weaker on the right than on the left. Reflexes were equal and active. Sensation was normal.

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*Course.*—The following day the right ankle joint was strikingly tender and swollen. The patient was transferred to another hospital with a diagnosis of acute rheumatic fever. The subsequent course was that of rheumatic fever.

*Comment.*—The presence of neck and back stiffness, hamstring spasm, and apparent weakness of dorsiflexion of the foot caused suspicion of poliomyelitis. The reflexes remained normal, however. The advent of frank arthritis and the absence of spinal fluid abnormalities were of diagnostic aid.

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Family history was irrelevant. The patient's past history was negative except for the occurrence of mumps at the age of 3 years.

*Physical Examination.*—Temperature was  $105^{\circ}$  F., pulse 110, respiration 25.

Over the entire body, less dense on the extremities than on the face and trunk, were slightly raised, discrete, pink papules 0.5 to 1.0 cm. in diameter. Dried blood was noted in the right nostril. The gums were spongy and bled easily. There were very small white ulcers on the gums and buccal mucosa. The tonsils were enlarged and reddened, but no exudate was present. The neck was slightly stiff and pain was produced on forward flexion. The lungs were clear. The heart was not enlarged. A short systolic murmur was heard over the entire precordium. The abdomen was normal. The back was limited in forward flexion. Kernig's sign was questionably positive bilaterally. The extremities were normal. The reflexes were equal and active. Motor power and sensation were unimpaired.

negative diplococci on culture. He was lethargic, uncooperative, and the neck was stiff. The patient was placed on full doses of sulfadiazine and became afebrile in twenty-four hours. His recovery was complete and uneventful.

*Comment.*—This case reveals the necessity of considering meningococcic sepsis in patients with polyarthritis with a high swinging fever that does not respond to salicylates. The rash often is confusing because purpuric lesions occur in both diseases. This case illustrated the difficulty in obtaining a positive culture in meningococcemia despite frequent examinations. The striking response to sulfadiazine in contrast to the indifferent response to penicillin is noteworthy and confirms present opinion as to the relative value of the use of sulfadiazine in meningococcic infections.

#### DISCUSSION

Although rheumatic fever and infection of the central nervous system may occasionally bear considerable mutual resemblance, their differentiation is rarely difficult if both possibilities are seriously considered. In most instances, the appearance of frank joint involvement will promptly exclude the diagnosis of poliomyelitis. Tenderness, swelling, and pain on motion of joints should be sought daily. Before joint manifestations are well marked, spasm of muscles in the area may mimic that which is commonly seen in poliomyelitis. Similarly, unwillingness to move an extremity because of pain may be mistaken for true muscular weakness, especially in young children. In association with the muscular weakness of poliomyelitis, depression or absence of deep reflexes invariably occurs. Depression of deep reflexes in an extremity involved by rheumatic fever does not ordinarily occur. The examination of the cerebrospinal fluid will settle diagnostic doubt in most instances. With the possible rare exception of increased spinal fluid protein, the findings in rheumatic fever are negative. The spinal fluid pleocytosis of poliomyelitis, on the other hand, is occasionally absent.<sup>9</sup> Myocarditis, especially as evidenced by abnormalities of the electrocardiogram, is of common occurrence in rheumatic fever, but occasionally may occur in either poliomyelitis or meningitis.<sup>10</sup>

The sedimentation rate is rarely elevated to a great degree in poliomyelitis, whereas the reverse is generally true of rheumatic fever. Moreover, the relief of pain afforded by salicylates in rheumatic fever is uncommonly duplicated in poliomyelitis. In the absence of salicylate administration the fever of rheumatism tends to persist for prolonged periods in many cases. In contrast, the fever is almost never elevated for more than a week in poliomyelitis. Indeed, the average duration of elevated temperature in hospitalized patients is less than one day.<sup>9</sup> In cases where initial doubt as to the diagnosis exists, repeated clinical observation with specific intent during a short period generally will establish the correct nature of the disease. Serial electrocardiograms are often of value.<sup>11</sup>

Although less frequently confused, the differentiation of rheumatic fever from meningococcus infections may be more difficult in those cases where frank meningitis develops after a prolonged period of arthritis or develops not at all. The intermittent, croplike eruption of the rash of meningococcemia, usually associated with spiking fever as well as the almost invariable inclusion of petechial



demonstration of a positive blood culture. In our experience patients with acute meningococcemia without meningitis have developed manifestations of myocarditis which might further cloud the issue. The picture in this patient was similar to that in Case 6, who was considered to have rheumatic fever. In this patient, the positive blood cultures were diagnostic.

CASE 8\*.—L. O. P., a man aged 24, was admitted to the Naval Hospital, Oakland, on Feb. 23, 1945. He had had rheumatic fever in April, 1944, at the Naval Training Station at Farragut and review of his record indicated that the course had been quite typical. On the present admission he had slight swelling, redness, and tenderness of the ankles and knees, of four days' duration.

*Physical Examination.*—Temperature 102.6° F., pulse 70. The knees and ankles were slightly swollen and tender. The heart was negative.

*Laboratory Examination.*—Complete blood count was normal. Sedimentation rate was 24 mm. The electrocardiogram was normal.

*Course.*—The patient was placed on full doses of salicylates and put to bed with a diagnosis of rheumatic fever. On February 24 it was noted that he had small, nonraised, painless, purplish areas on his extremities. He felt better and his joint pains were minimal; the temperature was 99° F. The eruption was interpreted by the dermatologist as being consistent with that seen in rheumatic fever. On February 25 a generalized, discrete, mildly erythematous eruption was seen, with predilection for the extremities. The lesions varied in diameter from 4 to 12 mm. He was afebrile on this day. Beginning on February 26, he began to have an intermittent fever to 102° F. and higher. Since a spiking fever is definitely unusual in cases of rheumatic fever, he was thoroughly examined again. The heart and lungs were normal on repeated examinations, as were the electrocardiogram, roentgenologic examination of the chest, and throat cultures. Repeated blood cultures also were negative. The electrocardiogram showed a low T<sub>1</sub> and T<sub>2</sub> on March 12, but no other abnormalities. A Weil-Felix test was negative, as were repeated urine examinations, including tests for porphyrin. Agglutination tests and examination of stools remained negative. On March 19 medication by salicylates was stopped and on the next day the arthritis became more prominent with pain and slight swelling of the ankles, toes, left wrist, and fingers. The rash had faded somewhat, leaving brown pigmented areas. On March 21, the polyarthritis was more severe. The blood sedimentation rate was 35 mm., the Addis test and urological smear were negative, and a urine culture revealed a scanty growth of a slightly hemolytic *Staph. aureus*. On March 23, the patient felt worse, had a temperature of 103° F., and a new crop of macular erythematous lesions appeared maximally on arms and legs. He now complained of slight headache and on examination his neck was slightly stiff but Kernig and Brudzinski signs were negative. He was started on penicillin, 20,000 units every two hours. He improved somewhat and within forty-eight hours his temperature fell to 99.2° F. the rash was fading, and the joint pains were less. A bromsulfalein test at this time revealed 30 per cent retention of the dye in an hour. Intravenous urograms were negative, as was a tuberculin skin test. On March 29, his temperature was 101° F., and he had headache and a stiff neck although the Kernig sign was negative. A blood culture in broth now revealed an organism resembling *Micrococcus catarrhalis*. The next day the patient was irritable, the frontal headaches were worse, but the skin had cleared. A lumbar puncture revealed an opalescent fluid under increased pressure without block; there were 1,000 cells, all polymorphonuclear, a total protein of 40 mg. per cent, sugar 48 mg. per cent, chlorides 693 mg. per cent. On March 31 his cerebral symptoms were worse. Spinal fluid smears were negative but showed gram-

\*This case was previously reported by Martin, W. B. and Snell, A. M.: Proc. Staff Meet. Mayo Clin. 20: 369, 1945.

# THE EMOTIONAL PROBLEMS AND EDUCATION OF HOSPITALIZED CHILDREN

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AS A RESULT of studies of emotional problems, nurses and pediatricians are becoming increasingly aware of the meaning of children's maladjustments, and are learning about the development as well as the recognition and treatment of these disturbances. The nurse's duty today is not, as formerly, merely to be concerned with the physical needs of the child. Her education has been extended to include training in seeing the child as a total individual, realizing many of his problems, and understanding many of the difficulties which puzzled her older colleagues. Today's pediatric ward is often equipped with many devices and staffed by many persons who, twenty years ago, would have been considered hygienically unclean and unsafe for the child. Pediatricians and surgeons are realizing that these new staff members as well as the new materials in pediatric wards are as necessary a part of the equipment as are the syringes, the medications, and the surgical instruments.

As to the education of children during their hospitalization, very little organized teaching was done during past centuries and probably little in this century until recent years. Margaret A. Rogers,<sup>1</sup> in 1938, reported the results of questionnaires from eighty-one children's hospitals and children's departments in general hospitals. School work was provided in fifty-three, occupational therapy in four, recreational therapy in two, and in twenty-two there was no teaching program of any sort reported.

Actually, in discussing the education of hospitalized children it would seem that we need concern ourselves only with the education of children with subacute or chronic conditions. While it might seem that educating a child during his convalescence from an acute illness may be of benefit in keeping him busy, it may also produce certain negative feelings about education which might remain with him for a long time.

The subacute and particularly the chronically ill child, on the other hand, unquestionably needs education while he is hospitalized. It is just as unwise to allow a child, to be inactive during his hospital stay, as it is an adult. During the recent war we saw how much emphasis was placed upon vocational rehabilitation, occupational therapy, and education of soldiers in our Army hospitals.

Since the child of 5 or 6 years and older is ready to spend most of his day in school, it would appear that his education should be of major importance during his free time in the hospital. When a child approaches this age he is ready to be taught and actually needs teaching for its emotional value to him.

From the Institute for Juvenile Research, Chicago.  
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elements in the rash, will, as a rule, allow differentiation from erythema marginatum. Repeated blood cultures may be necessary on occasion before the meningococcus is recovered. The appearance of frank meningitis associated with a purulent spinal fluid whose sugar content is sharply reduced, and from which the infecting organism usually may be cultured, is sufficient to dispel all doubt. It must be borne in mind, however, that myocarditis frequently occurs in the course of meningococcal infections,<sup>10</sup> and that electrocardiographic abnormalities must be viewed critically in the light of the total clinical picture before being accepted as a diagnostic criterion.

#### CONCLUSIONS

1. Stiffness of the neck and/or of the back, a positive Kernig's sign, and muscle spasm may occur at the onset of rheumatic fever and lead to the erroneous diagnosis of poliomyelitis or meningitis.

2. Lack of movement of an extremity, because the pain of rheumatic arthritis makes the patient unwilling to move it, may simulate the muscular weakness of poliomyelitis.

3. The appearance of frank, localized involvement of joints, the demonstration of a rapid sedimentation rate, the occurrence of myocarditis or dramatic response to salicylates are usually of aid in making the diagnosis of rheumatic fever.

4. The occurrence of spinal fluid abnormalities, the demonstration of depression or loss of deep reflexes in one or more extremities, the culturing of an organism from the blood or spinal fluid, or the appearance of true muscular weakness in an extremity are generally exclusive of the diagnosis of rheumatic fever.

5. The total clinical picture with repeated observations usually permits an accurate diagnosis to be made in doubtful cases.

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Experience at the Illinois Hospital-School for crippled children has shown that children often go through a testing period for the first several months after admission. One boy provocatively wondered on frequent occasions during the first ninety days he was there, "When do I get expelled from here?" When the staff, recognizing his acting out in two previous hospital stays, was able to be firm and consistent, yet tolerant, kind, warm, and sympathetic with him, he became a model patient in the space of about one year. His learning capacity, too, improved rapidly with this change.

Another child, 6 years old, who had never been encouraged to learn because her parents considered her to have an almost hopeless outlook, and who was, therefore, hindered from developing as she could, appeared upon admission to have the mental and emotional development of a 2½-year-old child. For several months after admission she even regressed to infantile behavior, wetting and soiling the bed, and requiring bottle feeding. The staff was quick to respond to her needs, accepting this bid for care on a baby's level, and after a few months, with patience and encouragement, this girl began to develop rapidly until she reached the emotional development of others of her own age.

The defenses a child uses when he comes into a new situation are often puzzling and bewildering to persons who do not understand the reasons. A formerly happy child may become blustering and defiant or sullen and withdrawn upon admission to a hospital.

Obviously, education in this first period of hospitalization is a difficult problem. Since it is up to the initiative of the child, a defiant, or sullen and withdrawn child will block any effort of the teacher to help him. On the other hand, motivation for learning may be strong enough so that a warm, sympathetic, and understanding teacher may bring the child to accept education in the hospital schoolroom or at the bedside while in all other activities he may be rebellious or passively withdrawn. To say that nothing can be done for such a child would be an error. One of the strongest motivations to learning is the teacher, who can establish a good relationship with a child in the somewhat neutral surroundings of books, pencils, and papers, while the nurse or physician may not be able to get close to him.

On our ward at the Illinois Neuropsychiatric Institute the teacher plays a very important part in the therapeutic program for psychologically disturbed children. Her value is often greater in this relationship than is the teaching she provides. Interestingly enough, it seems that improvement in a child's learning is largely dependent upon improvement of the teacher-child relationship.

After the first adjustment has been made, it is important to determine whether illness *per se* has had any effect on the child's ability to learn. It would seem that, except for children with brain injury or disease, the problems of educating hospitalized children are mainly psychological. Of those with organic injury of the brain, L. Pierce Clarke<sup>2</sup> remarked, "In other words, various forms of emotional arrest arising out of the reaction to organic injury fail to add impetus to the power of mental functioning; or they may positively

Education is, perhaps, the best sublimation for a child following the tremendous developmental problems he has handled from birth up to the time he enters school. All the energies which he has used in working out his feelings about himself as well as about the world around him, particularly his parents, his siblings, and his playmates, now need expression and engagement in constructive work. The best place for him to learn is in the school, and so his pent-up energy is transferred from the persons and objects surrounding him and from his curiosity about them into play and on into the text and teaching materials of the schoolroom. The teacher, then, becomes a sort of mother to him, a person who will help him to grow up and to learn.

When we discuss the education of the hospitalized child of educable age we must understand the differences between bedside teaching and teaching in groups in the average schoolroom. Children learn not only because they want to please their teacher as well as their parents, but also because of certain competitive feelings. A child learns not only by reading a book, seeing a blackboard, or hearing what the teacher has to say, but also by hearing what Johnny has to say in the same room on a given topic, and by trying to outdo him. It is quite clear, then, that bedside teaching without this competition poses certain problems which have to be met and understood by the bedside teacher.

When a child leaves his home for a hospital, he faces a number of new problems. The main one is this leaving the home with all that it implies. Even the adolescent who leaves home for a hospital must face the prospect of new adults to whom to look for the satisfactions he sought in his parents. "What will these new people be like?" the child wonders. "What will happen at home while I am gone?" If there are siblings in the home the child may worry that they might make their position more secure and perhaps displace him when he returns. He wonders if this leaving the home is, perhaps, a punishment for having done "bad" things which he supposes some of his acts to be, and whether the parents, by requiring hospitalization, are disowning him because of minor infractions of home rules which he, in his childish mind, believes to be serious? Perhaps his fantasies, because of some anxiety, are vivid and destructive, so that he thinks being hospitalized is punishment. There seems to be in most children more concern about leaving the home and going to a strange environment than concern about the illness itself. The child also wonders how he should act toward these new adults, and, depending on how he has gotten along with adults prior to his hospitalization, he will face the new experience with more or less concern.

Then there is the disease itself. The child may wonder what will happen. "How will the disease be treated, and what does it mean? What about the other children in other beds? What is wrong with them and why are they there?" But more important, the child wonders and often expresses his anxiety as to what those children think of him. "How am I going to get along with them?" "Will they like me?" Childhood is always a matter of bewilderment, confusion, testing, concern, and curiosity. Children are always posing the problem to themselves of how they will get along in a group and whether they will be liked.

Experience at the Illinois Hospital-School for crippled children has shown that children often go through a testing period for the first several months after admission. One boy provocatively wondered on frequent occasions during the first ninety days he was there, "When do I get expelled from here?" When the staff, recognizing his acting out in two previous hospital stays, was able to be firm and consistent, yet tolerant, kind, warm, and sympathetic with him, he became a model patient in the space of about one year. His learning capacity, too, improved rapidly with this change.

Another child, 6 years old, who had never been encouraged to learn because her parents considered her to have an almost hopeless outlook, and who was, therefore, hindered from developing as she could, appeared upon admission to have the mental and emotional development of a 2½-year-old child. For several months after admission she even regressed to infantile behavior, wetting and soiling the bed, and requiring bottle feeding. The staff was quick to respond to her needs, accepting this bid for care on a baby's level, and after a few months, with patience and encouragement, this girl began to develop rapidly until she reached the emotional development of others of her own age.

The defenses a child uses when he comes into a new situation are often puzzling and bewildering to persons who do not understand the reasons. A formerly happy child may become blustering and defiant or sullen and withdrawn upon admission to a hospital.

Obviously, education in this first period of hospitalization is a difficult problem. Since it is up to the initiative of the child, a defiant, or sullen and withdrawn child will block any effort of the teacher to help him. On the other hand, motivation for learning may be strong enough so that a warm, sympathetic, and understanding teacher may bring the child to accept education in the hospital schoolroom or at the bedside while in all other activities he may be rebellious or passively withdrawn. To say that nothing can be done for such a child would be an error. One of the strongest motivations to learning is the teacher, who can establish a good relationship with a child in the somewhat neutral surroundings of books, pencils, and papers, while the nurse or physician may not be able to get close to him.

On our ward at the Illinois Neuropsychiatric Institute the teacher plays a very important part in the therapeutic program for psychologically disturbed children. Her value is often greater in this relationship than is the teaching she provides. Interestingly enough, it seems that improvement in a child's learning is largely dependent upon improvement of the teacher-child relationship.

After the first adjustment has been made, it is important to determine whether illness per se has had any effect on the child's ability to learn. It would seem that, except for children with brain injury or disease, the problems of educating hospitalized children are mainly *psychologic*. Of those with organic injury of the brain, L. Pierce Clarke<sup>2</sup> remarked, "In other words, various forms of emotional arrest arising out of the reaction to organic injury fail to add impetus to the power of mental functioning; or they may positively

interfere with the reception and retention, as well as the use of knowledge." If this concept is correct, and our experience at the Hospital-School seems to bear it out, then it is of major importance in educating patients with cerebral palsy as well as with other organic diseases of the brain. With regard to the treatment of these patients, Clarke noted that they should be treated from a total point of view and he added significantly: "Concealed and psychological factors, too, have an important place—both on their own account and for their influence upon the success of other approaches."

The total staff attitude toward children poses another problem. If a child is looked upon as an individual at his age level or at least at his optimum emotional age level, then stress upon his maintaining a mature attitude will help him to accept education as he would be expected to do if he were well and at home living with his parents. But hospital routines are often rather strange. Marion Strauss<sup>3</sup> remarks, "Closely associated with this curbing of initiative through thwarting is the docility developed by hospital routine and physicians' instructions. Much of the crippled child's life is circumscribed by regimentation imposed upon him. Cooperation with medical authority is applauded; docility is encouraged as necessary to the physical well-being of the child, and docility and initiative do not develop in the same soil!" It seems obvious, therefore, that a routine which requires a docile attitude from the child should not at the same time expect from him aggressive, enthusiastic interest in learning. The most excellent teacher, able in techniques and personality, can do little in such an atmosphere. A child's motivation is largely the result of adult attitudes in his environment, but it is also the result of his competitiveness with other children. Since in bedside teaching particularly and in the very small group teaching of many hospitals there is a lack of competition, only adult attitudes are left as the primary source of motivation for the child. The teacher's problem in this situation is not only her own, but a staff problem as well, and must be discussed on a staff basis just as any other of the child's problems is best handled by group discussion and consultation to work out plans and formulate policies for the child. Miss Ingersoll, in her discussion of Miss Rogers'<sup>1</sup> paper, points out the need for such conferences to establish rapport of all the workers.

The teacher who works in a hospital should be equipped to accept a kind of child different in certain ways from those she sees in the average school-room. She should be reasonably stable emotionally, able to accept infantile demands as well as passive, withdrawn, and defiant, provocative attitudes on the part of otherwise normal children, without being too disturbed. Miss Ingersoll emphasizes this point by remarking that the teacher should be a "well-adjusted person who has a knowledge of the expectancies of children at different age levels and of individual sick children; a person who does not project his own feelings; one who has objectivity of attitude and behavior and the ability to see things as they are." This is a very difficult task for even the most healthy individual, and it is particularly difficult for the teacher who is anxious and easily irritated to be faced with this kind of child. The staff

conference, then, becomes a good source of exchange of ideas and a discussion of mutual difficulties with children. The staff conference is of further value. New teachers, nurses, occupational therapists, etc., often become discouraged and feel inadequate when they fail to help children who are entrusted to their care. The opportunity to sit down at a conference table and discuss problems of mutual interest is a tremendous relief for these new people as well as an opportunity for pooling ideas, and for the formulation of new approaches to a child with problems. This technique used by the psychiatrist, psychologist, and social worker in our child guidance clinic is used also by the doctor of physical medicine—the rather new specialty which has developed in medicine. This physician, too, believes in the total approach to the patient and encourages a mutual exchange of problems and ideas by the staff. There are other physicians, however, who are not used to this method because the proper practice of medicine requires physicians to make their own decisions, with the result that pooling of ideas with nonprofessional persons is difficult. Most doctors are, however, responsive to the new ideas, although it sometimes takes patience and education on the part of the hospital staff to bring about a change of attitude. The development of a new idea such as that of combined staff conferences in an old, established, routinized hospital or similar institution, is a difficult problem. This is not always the case, but it is true often enough to present a problem for those persons working in this type of institution when they attempt to make any change which might appear drastic. The manner in which one can bring about these changes depends upon one's self, one's associates, as well as the total staff outlook in the institution.

#### SUMMARY

Most children who are hospitalized with subacute or chronic illnesses and are educable in so far as age and intelligence are concerned seem to require education as a part of their normal development. The problems involved in educating hospitalized children do not, therefore, seem far different from those experienced by teachers in the usual classroom. The main difficulties arise during the earlier periods of hospitalization when the child is adjusting to the new group of children and adults, as well as working through his anxieties and fantasies regarding his separation from his home. Once the child is established in the new group, the problems facing the teacher are, for the most part, those of staff attitudes reflected in the children and not basic neurotic difficulties of the child himself.

A cursory review of the literature leaves the impression that many of the problems involved in educating hospitalized children require considerable study. The teacher in a children's hospital or institution faces problems arising from an environment strange not only to the children but also to herself, so that she must of necessity use enterprise, courage, and initiative in developing new techniques. Study of the various methods to be used and the obstacles encountered should be a part of every hospital teacher's plan when she begins work in this type of institution. Only by study and research and the



reporting of all the various aspects of teaching subacute and chronically ill children can we arrive at a greater understanding as we move toward a more healthy attitude on the part of adult hospital personnel toward the child patients.

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#### Addendum

Since this paper was read the writer received a publication which he would recommend to persons interested in the education of hospitalized children: "Advancing the Education of the Hospitalized Child." National Foundation for Infantile Paralysis. 120 Broadway, New York 5, New York. Publication No. 72.

## Case Reports

### PERITONITIS DUE TO INGESTION OF GLASS CHIPPED FROM BABY-FOOD CONTAINER

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CONSIDERING the prevalent use of food from glass containers, particularly for infant feeding, it is surprising that more accidents due to the ingestion of glass chips from these containers are not recorded in the literature. It is believed advisable to report the case of a 13-month-old infant who developed peritonitis following the ingestion of glass chipped from a baby-food container.

#### REPORT OF CASE

*History.*—M. D., aged 13 months, was admitted to the West Suburban Hospital on Aug. 14, 1948, at 2 A.M., with the following history: On the previous day he awoke happy and playful. At 8:30 A.M. he began to scream, assumed a doubled-up position, and vomited. The pain in the abdomen apparently became worse on moving the patient or by palpation of the abdomen. A physician was consulted by telephone at 11:30 A.M. because there was no spontaneous relief of the symptoms and the child had vomited several times. Two teaspoons of milk of magnesia were prescribed and given without apparent benefit. The patient was restless and irritable. The mother had given six enemas between 9 A.M. and 2 P.M. for "stomachache." With the return of the last enema there was approximately one tablespoonful of clots of bright red blood. The stools had been soft brown during the preceding week. At 3 P.M. it was noted that the infant had a fever of  $101^{\circ}$  F. per rectum. Another doctor was telephoned at that time and he suggested that the blood might have resulted from too many enemas and advised that the infant have nothing by mouth for five hours and then be allowed to have 2 ounces of milk. At 10:30 P.M. the latter physician's associate called at the home and found that the abdomen presented marked tenderness and no bowel sounds could be heard. Because of the marked abdominal pain, marked tenderness of the abdomen, and the history of clotted blood in the stool, a tentative diagnosis of intussusception was made and the patient was hospitalized.

*Hospital Course.*—Forty-five minutes after admission, anesthesia was induced with ether and the abdomen was explored through a right paramedian incision. The small bowel was markedly distended with gas. There was a moderate, thin, cloudy, seropurulent exudate free in the peritoneal cavity. No intussusception was located. The appendix was covered with a shaggy, grayish-white exudate, as was the adjacent cut, including the cecum and terminal ileum. Routine appendectomy was performed and ligation was made with purse-string suture of the stump. The abdomen was closed without drainage.

The child's postoperative course was stormy because of the peritonitis observed at surgery. Penicillin, crystalline G, 30,000 units intramuscularly every three hours and sodium sulfathiazole 2.5 Gm. daily in intravenous fluids were given. When the patient failed to respond to this therapy thirty-six hours after surgery, in addition, he was given streptomycin 0.4 Gm. every eight hours.

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Wangensteen suction was necessary because of vomiting and continued distention. During the first twelve hours the material aspirated contained partially digested blood in moderate amount from the stomach.

At 10 A.M. and 4 P.M. on Aug. 15, 1948, the patient passed moderate amounts of hard-formed stools with streaks of bright red blood. Rectal examination at 5 P.M. revealed a small amount of light brown stool containing flecks of blood with a sliver of glass 27 mm. long, sharply pointed, in it. The piece of glass resembled that which might have been chipped off the rim of a glass container which contained baby food. It was suggested to the mother that she attempt to locate the bottle which was chipped. The following day, the mother returned with a glass container about one-third filled with puréed apricots which had a defect on the rim which the glass chip fitted perfectly. The mother then gave the history of opening the jar and feeding the infant material from this container at 6 P.M. on Aug. 12, 1948. There was no gagging or choking at that time.

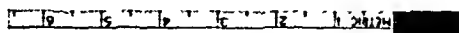


Fig. 1.—Photograph of glass container with chipped rim and corresponding glass fragment which had been ingested by 13-month-old infant.

An x-ray film of the abdomen taken on Aug. 14, 1948, failed to reveal the piece of glass as radio-opaque. The temperature rose to 102° F. on the second hospital day and gradually returned to normal by the fifth postoperative day. The bowel sounds returned and distention subsided on August 17. At that time Levine tube aspiration and intravenous fluids with sulfathiazole were discontinued. Penicillin and streptomycin were continued through August 20. The remainder of the hospital course was not remarkable.

*Tissue Report.*—Gross description of the specimen consisted of an appendix measuring 40 × 5 mm. The serosa was grayish-white; in areas it was shaggy. The mucosa was white. Microscopic findings revealed that the glands were

numerous. The mucosa contained eosinophiles. Lymph follicles were numerous with active germinal centers. The serosa was covered with a thick layer of fibrin with numerous polymorphonuclear neutrophils and round cells. The adjacent muscularis was infiltrated with similar cells. Pathologic diagnosis was follicular hyperplasia with severe periappendicitis.

The history, abdominal findings at surgery, the postoperative course, the pathologic examination of the appendix, and the recovery of the glass foreign body indicate that the patient developed peritonitis secondary to perforation of the bowel by a glass fragment from a baby food container. No evidence of primary appendicitis was observed.



Fig. 2.—Photomicrograph of appendix showing follicular hyperplasia and severe periappendicitis.

#### DISCUSSION

The history of the accident was not obtained until after the passage of the piece of glass from the rectum following surgical intervention. This patient presented features which made an accurate diagnosis difficult. According to Ladd and Gross, appendicitis is quite rare in the first year of life, and is infrequently found in the second year, but from then on it becomes common.<sup>1</sup> The history and physical findings in this case led the surgeons to consider the pre-operative diagnosis of intussusception. Steele<sup>2</sup> presented two cases of mediastinitis which followed the ingestion of glass in baby food from containers from which glass had been chipped when the containers were opened. It is probable that the glass fragments from the containers result from improper exertion of force at one particular point in prying the covers off the vacuum-packed glass containers. Careful prying of the lid from these containers at more than one point and inspection of the jar rims by the mother after opening them are recommended as safety measures.

The type of chip which fragments from the rim of a glass container tends to have sharp edges and points which may result in perforation of the gastrointestinal tract at any level. The presence of this type of foreign body as the cause of bleeding through the mouth or anus or of signs of mediastinitis or peritonitis should be considered. Residual defects in the baby food or other containers should be sought in an attempt to rule out this possibility.

#### SUMMARY

A case of peritonitis in an infant resulting from perforation of the bowel by a glass fragment from a baby-food container is reported. When hemorrhage from the gastrointestinal tract is a presenting symptom, accidental ingestion of a sharp chip from the rim of a glass container should be considered as an etiologic possibility. Safety measures preventing this type of accident are emphasized.

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## HYCODAN (DIHYDROCODEINONE) POISONING

### COMPLETE RECOVERY FOLLOWING AN INITIAL COMA OF FIFTEEN HOURS IN A THREE-YEAR-OLD CHILD

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**A**N EXAMINATION of the literature fails to reveal any reports of Hycodan Bitartrate poisoning. This product, a bitartrate salt of dihydrocodeinone, was introduced in this country in 1942 from Germany, where it had been used under the name of Dicodid. Several reports have appeared in the American literature in which it has been described as being a more "active analgesic and cough sedative than codeine, but a less active one than morphine."<sup>1</sup>

The following is a case report of a 3-year-old infant admitted to the Beth El Hospital in a state of coma which persisted for fifteen hours, and was associated with marked hyperglucemia, glycosuria, and acetoneuria.

#### CASE REPORT

H. G., a white male child, aged 3 years and weighing 41 pounds, was admitted to the pediatric service at noon on May 15, 1948, in an unconscious state.

The child had taken his usual 10 A.M. milk, at which time the mother noticed that the boy appeared tired and he was put to bed. About forty minutes later she heard the child sighing deeply. The mother attempted to arouse him but finding that he did not respond she brought him to the hospital where he was admitted through the emergency room.

On admission the child was found to be in a deep coma and unresponsive to external stimuli. He was markedly cyanotic with the respiratory rate two to three breaths per minute. No ecchymosis, hematoma, petechiae, or injury were noticed on the surface of the body. The fontanelles were closed, and no masses were palpable or visible on the skull. The pupils were pin-point and apparently did not react to light. The conjunctivae and sclerae were clear. The pharynx, tongue, and mucous membranes of the mouth were normal. The neck was supple with no rigidity or limitation of motion. There were no palpable cervical glands.

The chest showed very little expansion bilaterally, but was normal to percussion and auscultation. No râles or adventitious sounds were heard. The heart sounds were regular, of good quality, and the rate was 70 beats per minute. The blood pressure was 126/56 mm. mercury. The abdomen was soft with no palpable masses present; the liver and spleen were not enlarged. The external genitalia were normal and both testes were present in the scrotum. The child displayed a complete areflexia. Kernig, Babinski, and Brudzinski signs were not elicited.

The impression at this time was that the patient was possibly suffering from a poisoning. He was given emergency treatment consisting of artificial respiration, oxygen inhalation by mask, and gastric lavage. The returns from the lavage consisted of a pinkish fluid which, upon later examination, proved to contain pierate of codeine. The child was also given stimulation therapy consisting of hypodermic injections of caffeine sodium benzoate ( $\frac{1}{2}$  c.c.) and 5

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minims of adrenalin. In the meantime the mother was questioned rather carefully regarding the possibility of the child's access to poisons. It was then learned that on the morning of admission the child had been playing with a bottle containing the undiluted mixture of the Syrup of Hyecodan Bitartrate which had been prescribed for an older member of the family. Two and one-half ounces of the original 3 ounces were missing from the bottle.

Meanwhile laboratory reports were being received. A catheterized specimen of urine revealed the presence of 4 plus sugar, 4 plus acetone, specific gravity of 1.020, negative albumin, and no casts or blood cells. The blood count showed a hemoglobin of 71 per cent, 3.7 million red blood cells, 20,000 white blood cells, of which 43 per cent were polymorphonuclear cells. The blood sugar and urea were 400 mg. and 15.7 mg., respectively, and carbon-dioxide combining power was 45 volumes per cent. The spinal fluid was found to be clear under normal pressure. No increase of cell protein or chloride but a sugar of 133 mg. per cent was noted. The culture and smear were subsequently reported as negative for organisms. A blood culture taken on admission was reported to be negative after forty-eight hours. A portable x-ray examination of the chest showed no evidence of parenchymal infiltration or pleural involvement.

Two hours after admission the child's condition had not changed materially. Gastric lavage was repeated with several ounces of the "universal antidote" consisting of one part of tannic acid, one part of magnesium oxide, 2 parts of charcoal being added. In view of the slow and shallow respirations  $\frac{1}{250}$  grain of atropine sulfate was given by hypodermic injection. Within one-half hour the temperature rose to 103° F., the facies became flushed, and the respirations grew quite rapid. At this time the child began to twitch slightly, although no gross convulsive seizures were noted. The child was given 50,000 units of penicillin every three hours. A continuous intravenous infusion of normal saline solution was started.

A blood sugar determination taken three hours after admission was 181 mg. per cent of blood, the urine still showed 4 plus sugar and 4 plus acetone. Six hours after admission the blood sugar was 96 mg., but there was still 2 plus sugar and 4 plus acetone in the urine. The child was still comatose and breathing heavy. A solution of 5 per cent glucose in saline was substituted for the original saline fluid used in the venoclysis. Also 10 c.c. of Betalin and 250 mg. of ascorbic acid were added to the solution.

Fifteen hours after admission the child began to respond. His respirations at that time were 28 per minute, the pulse was irregular and bounding, but the color was still poor. Gradually the child became more alert. The pupils began to dilate and react to light and accommodation. The improvement was progressive and the next day the child responded coherently. The following day the child returned to a normal state of well-being.

On the fourth hospital day he developed signs of a broncho-pneumonia which were confirmed by x-ray. The penicillin therapy was continued and within seventy-two hours all signs of the pulmonary involvement had disappeared. Nine days after admission the patient was discharged from the hospital in apparently good condition.

Further laboratory data taken after the initial emergency tests were: cephalin flocculation 1 plus after eighteen hours, zine turbidity 7 units, Wassermann negative, glucose tolerance curve (third hospital day) was within normal limits. The urine examination on the second day after admission still revealed 4 plus acetone, negative to sugar. Subsequent examinations of the urine were completely negative. An electrocardiogram taken on the fifth day of illness revealed a sinus tachycardia with well-marked sinus arrhythmia, but there were no abnormalities suggestive of myocardial changes.

## COMMENT

Careful history taking in cases of poisoning is essential. It was only after one-half hour of close questioning of the family that the mother volunteered the information that the child had been playing with the Hycodan mixture. This again brings to the fore the necessity of warning parents of the inherent dangers in leaving opiate-containing drugs within the reach of children.

In view of the hyperglycemia and 4 plus glucose and acetone in the urine we thought that we might be dealing with a dual condition of diabetes mellitus plus poisoning, and the question of insulin therapy was considered. But treatment of a possible diabetic condition was held in abeyance until the results of the carbon-dioxide combining power was reported. When this was found to be 45 volumes per cent, and the repeat blood sugar 181 mg., we felt that the disturbance in carbohydrate metabolism was secondary to the toxic effects of the drug.

## SUMMARY AND CONCLUSIONS

An overdosage of Hycodan Bitartrate taken accidentally by a child produced a clinical picture similar to that found in morphine poisoning. Hyperglycemia with glycosuria and acetonuria were part of this clinical entity. Although the child was unconscious for fifteen hours, ultimate complete recovery was obtained.

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# FATAL HOMOLOGOUS SERUM HEPATITIS IN A YOUNG INFANT

## CASE REPORT WITH NECROPSY STUDIES

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REPORTS of fatal homologous serum hepatitis occurring in infants are extremely rare. A case of hepatitis in a 10-month-old girl seventy-one days after the administration of measles convalescent serum was reported in England in 1943.<sup>1</sup> Homologous serum hepatitis occurring in a 3½-month-old baby boy sixty-one to 101 days after multiple whole blood transfusions for neonatal anemia, with fatal termination, was reported by Wood and Black.<sup>2</sup> Bruyn<sup>3</sup> traced a fatal case of hepatitis, in a 15-week-old male infant, which he believed to have resulted from multiple transfusions of whole blood for the treatment of erythroblastosis sixty to 100 days before the onset of the disease. These were the only instances found in the literature; therefore, this case with necropsy studies should be worthy of record.

### CASE REPORT

This white male infant was born at term without difficulty on Jan. 30, 1948, following an uneventful pregnancy. The father and mother gave no history of any illnesses prior to, during, or after pregnancy. The child was breast fed with supplemental feedings started on the seventh day when he left the hospital. Shortly after going home the child developed impetigo of the abdomen and toes which was treated with a mercury ointment and cleared rapidly. About this time the child became constipated and was given enemas and prune juice without effect and finally Castoria, which produced a curdy stool. Several days following this episode he began to have foamy green liquid stools which were often bloody and were frequently nine to twelve per day in number. Occasionally vomiting and regurgitation of food was noted by the parents. On the nineteenth day of life the patient was seen by a physician who put him on a diet of weak tea and dextro-maltose peptin agar, as much as tolerated. Two days following that he refused all food and vomited the fluids taken. At this time fourteen watery stools were noted in one day. He was then admitted to another hospital where he was found to be dehydrated and acidotic and was treated with intravenous fluids, parenteral liver, and supplementary vitamins. Between February 20 and February 24 he received two transfusions of whole blood of 50 c.c. each, and three 75 c.c. pooled plasma infusions. Laboratory examination during this time showed a red blood count of 3,210,000 with a hemoglobin of 69 per cent, and white blood count of 8,800 with polymorphonuclear leucocytes 56 per cent, lymphocytes 42 per cent, monocytes 1 per cent, and eosinophiles one per cent. The admission carbon-dioxide combining power was 29 volumes per cent and the nonprotein nitrogen was 32.6 mg. per cent. The child improved rapidly and was discharged from the hospital on February 29.

The child was first seen in the clinic at Children's Mercy Hospital on March 29, 1948. The parents stated that the baby had been crying apparently without cause, as he did not appear ill. The physical examination was not remarkable and a change of formula apparently corrected the difficulty as he

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did not appear in the clinic again until April 30, 1948. At this time the parents complained that the child had a mild diarrhea and fever. Physical examination revealed a well-developed and well-nourished white male infant who appeared to be in mild distress with a questionably tense, nontender abdomen in which no masses could be palpated. The ears, skin, throat, and sclerae were clear, and the rectal temperature was 101.4° F. The child was given symptomatic treatment including iron and supplementary vitamins, A, D, and C. The diarrhea had subsided by the second hospital day and the temperature remained around 99° F. rectally throughout the remainder of the hospital stay.

X-ray examination of the chest showed that the lung fields were clear and the heart was of a transverse type with slight widening of the mediastinal shadows. The blood picture showed 3,310,000 red blood cells with a hemoglobin of 65 per cent (10 Gm. per 100 c.c.). The white cell count was 8,000 with 13 per cent polymorphonuclear leucocytes, 84 per cent lymphocytes, 2 per cent monocytes, and 1 per cent basophiles. Urinalysis revealed a specific gravity of 1.004 with rare white blood cells and occasional epithelial cells. The tests for albumin and sugar were negative. The child continued to improve and was dismissed from the hospital on the sixth day. It is interesting to note that on the day before dismissal and the day of dismissal he was seen by almost the entire resident staff and two visiting pediatricians, none of whom noted jaundice.

Late in the morning of the day after discharge from the hospital, the mother brought the infant to the outpatient department complaining that he had been quite fussy since shortly after arriving home. The external appearance of the child had changed markedly in the twenty-three-hour period since discharge. Intense jaundice was seen in both the skin and sclera. The neck was stiff and the upper extremities were rigid. Examination of the chest and throat revealed no abnormalities. A diagnosis of meningitis was made and the infant was readmitted to the hospital. A lumbar spinal tap showed no increase in pressure, and clear fluid with 5 white blood cells and 54 red blood cells per cubic millimeter was obtained. On the same specimen a sugar of only 18.9 mg. per cent was found. Smears and cultures did not reveal any organisms and the Pandy test was negative. The white blood count had shifted since the first admission so that the total white blood count was now 10,700 with 86 per cent polymorphonuclear leucocytes and 14 per cent lymphocytes. A soft, formed, yellow stool, passed shortly after admission, was negative for bile.

The condition of the child gradually became worse. Convulsions and opisthotonos developed. Eight hours after admission he began to vomit bloody material and pass small quantities of bloody stools. The highest temperature recorded was 101.2° F. rectally. Despite supportive therapy including intravenous sodium sulfadiazine, penicillin, streptomycin, vitamin K, and oxygen, he died eighteen hours after readmission to the hospital.

*Autopsy.*—The autopsy was performed four hours after death and a summary of the pertinent findings follows. The body was that of a well-developed, well-nourished, 3-month-old male infant measuring 58 cm. in length and weighing 4.6 kg. A moderate jaundice was present and the sclerae were yellow. The peritoneal surfaces were dry and the large intestine moderately distended with gas. The liver edge was well above the costal margin. The liver was slightly flattened, rather firm, and weighed only 60 grams, being approximately one-half the normal size for an infant of this age. The capsule was smooth. The cut section of the liver was quite pale in areas and where the liver lobules could be distinguished the centers were dark and the peripheral portions pale gray to almost white in color. The right lobe was mottled greenish-brown with loss of the lobular pattern over most of its surface. The gall bladder contained approximately 10 c.c. of clear mucoid fluid. The mucosa was white. The bile ducts were patent and were lined by white mucosa without any trace of bile staining.

The spleen was approximately twice normal size, weighing 25 grams, and had a tense capsule. On section the parenchyma was red and the Malpighian foci could not be distinguished clearly.

The esophagus was distended with reddish-brown material and bloody fluid. On the posterior mucosal surface of the lower end, numerous petechial hemorrhages were seen. The stomach was dilated with semi-fluid material similar to that seen in the esophagus. The remainder of the intestinal tract contained scattered masses of black material but the small intestine was not distended. Despite the history of bloody stools, no point of bleeding could be found in either the colon or rectum, although a moderate quantity of gas was present.

The kidneys together weighed 50 grams. The cut section was quite pale and everted. The boundary zones were distinct and the cortices slightly thicker than normal. No gross bile staining was encountered.

Examination of the cranial contents showed yellow stained meninges. The brain was pale and weighed 650 grams. The nuclei were not bile stained. The choroid plexi were delicate and surrounded by clear cerebrospinal fluid.

The heart weighed 32 grams. Beneath the epicardium, inferior to the auriculoventricular septum, over the left ventricle, were four minute hemorrhages. Several fine, hard granulations were found along the edge of the mitral valve measuring 1 to 4 mm. in diameter.

Each lung weighed 37 grams and was pink and air-containing with scattered petechial hemorrhages.

The thymus weighed 22 grams.

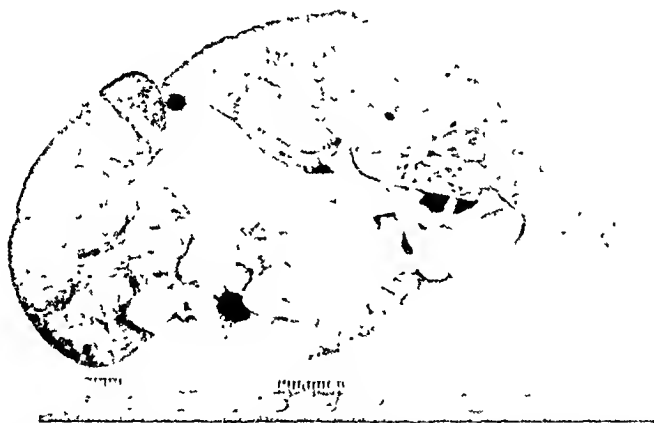


Fig. 1.—Cross section through the greatest diameters of the spleen and liver to show the small size of the liver and the enlarged spleen. The white mucosa of the gall bladder can be seen at the right.

*Microscopic Examination.*—Sections through the liver showed extensive destruction of the parenchymal cells so that the lobular pattern was obscured. The central veins were widely dilated or collapsed and frequently surrounded by clusters of red blood cells or masses of golden brown pigment. The sinusoidal pattern was lost, but some of the sinusoids were distinct, widened, and appeared to have degenerating liver cells attached to the stromal remnants. The bile ducts had proliferated most remarkably. In certain areas masses of apparently proliferating bile duct epithelium could be seen in clusters of twelve to twenty cells without any discernible lumen. These dense areas of proliferation seemed to be located in the periportal spaces. Many types of atypical liver cells were seen, ranging from mere shadowy cell structures to very large cells in which pink

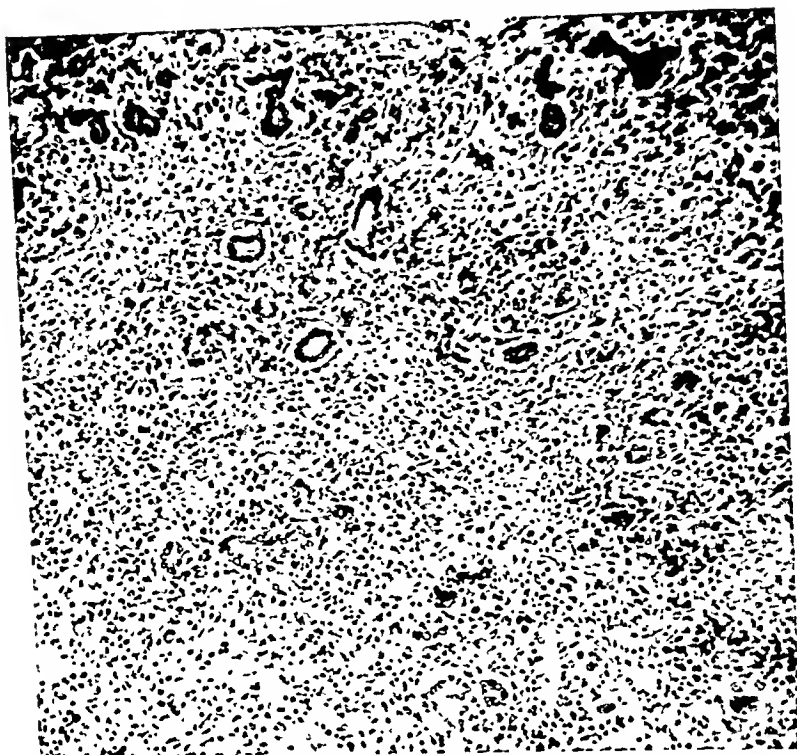


Fig. 2.—The liver shows marked proliferation of bile ducts and widespread destruction of liver cells. The clusters of hyperchromatic nuclei in the lower right probably represent foci of hemopoiesis. Low power.

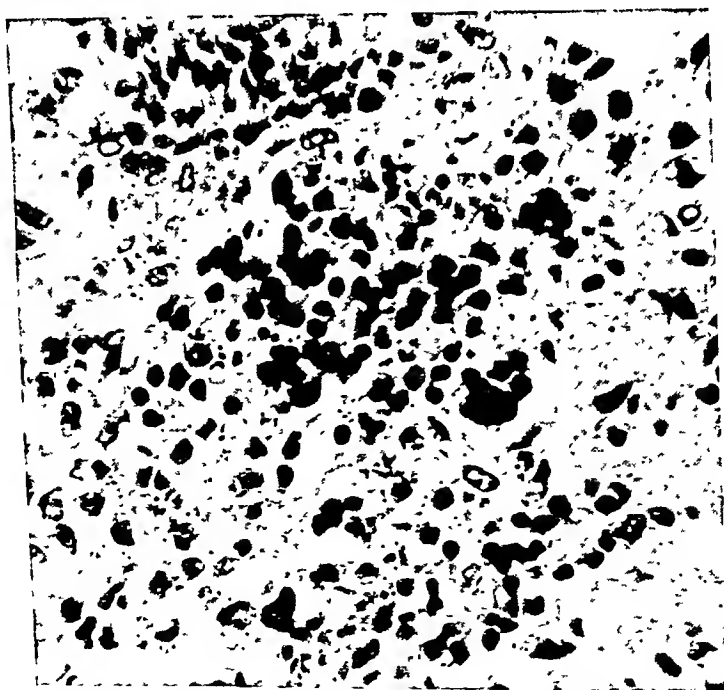


Fig. 3.—A cluster of cells in the liver with dark staining nuclei. The cells in the center appear to be a focus of hemopoiesis, while others probably represent regenerating liver cells. Cellular debris is present in many of the macrophages. High power.

staining cytoplasm and very dark nuclei were present. Many of these seemed to be forming open clefts completely detached from other cells. Groups of cells were hyalinized and stained uniformly with eosin. In these no nuclei could be found. Scattered in an irregular pattern there were clusters of cells with hyperchromatic nuclei, some of which were irregular and others of which had uniform, round, small nuclei. With the Giemsa stained preparations, these latter cells appeared to be nucleated red blood cells. Sections from different portions of the liver showed the same characteristics.

The kidneys showed tubular degeneration with marked vacuolization and swelling of the cells lining the proximal convoluted tubules, so that the lumina were practically obliterated by uniform red staining granular material. The blood vessels were widely dilated. An occasional hyaline cast was seen in the collecting tubules.

In scattered areas throughout the lungs the alveolar walls were thickened and in many alveoli small collections of monocytes were present. In other areas there were minute hemorrhages into the alveolar walls and occasional breaking into the alveolar spaces.

The pulp of the spleen was filled with red blood cells and the reticulo-endothelial cells were increased. Small foci of hemopoiesis were also present. A lymph node showed widely dilated sinusoids. Sections through the bone marrow of the sternum, rib, and vertebrae were hyperplastic as indicated by the marked cellularity and hemopoietic activity.

Slight degenerative changes were present in the ganglion cells of the brain.

#### DISCUSSION

The anatomic findings in this child were similar to those described by Lucké<sup>4, 5</sup> in a study of fatal hepatitis occurring in the United States Army in the epidemics of 1942 to 1945, as well as those described in many adult cases of fatal homologous serum hepatitis.

The massive destruction of the liver parenchyma with proliferation of the bile ducts is characteristic of the acute phase of the disease. The nephrosis, multiple petechiae, and gastrointestinal hemorrhage seem to substantiate this diagnosis. Furthermore, the administration of pooled plasma three times and whole blood on two occasions seventy-three and seventy-seven days before death provide an adequate incubation period for homologous serum hepatitis to develop. The incubation period is usually between sixty and one hundred thirty-five days with an average of about 100 days. The mild prodromal gastrointestinal symptoms are also frequently seen in this disease.

In addition to the rarity of this disease in infants, two other factors add to the interest of this case. The first is the mild prodromal stage of the illness, a minor gastrointestinal disturbance with recovery, which gave no indication of the destruction of the liver which must have been present when the infant was discharged from the hospital. The second is the sudden onset of jaundice and prostration as the icteric and terminal phases of the illness. In the three other reported cases the infants appeared to be doing quite well until shortly before death, which occurred suddenly and unexpectedly. In adults the beginning of the terminal phase is usually abrupt, but the transition most frequently occurs more than one week prior to death.

#### SUMMARY

A case of fatal homologous serum hepatitis occurring in a 3-month-old infant seventy-three to seventy-seven days following the administration of whole blood and pooled plasma is reported. The symptoms of the prodromal period

were gastrointestinal in type with diarrhea and vomiting but without jaundice. The terminal stage was sudden in onset with jaundice, multiple hemorrhages, and central nervous systems manifestations.

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## Clinical Conference

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STAFF CONFERENCE OF THE PEDIATRIC DEPARTMENT OF THE  
SALT LAKE COUNTY GENERAL HOSPITAL, COLLEGE OF  
MEDICINE, UNIVERSITY OF UTAH

JOHN A. ANDERSON, M.D., PEDIATRICIAN-IN-CHIEF

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ERWIN D. GOLDENBERG, M.D., CHIEF RESIDENT, PEDIATRICS

### Case 1. Poliomyelitis and Acute Salicylism

DR. ROBERT S. ELY (Fellow in Pediatrics).—The first case for discussion is that of a 20-month-old female infant, who was admitted with complaints of irritability, fever, and listlessness present five days prior to admission. Shortly after the onset of the fever, the child complained of pain in the legs, particularly when they were moved about by the parents. On the second day of the illness, consultation with the private physician revealed evidence of fever and an inflamed throat. Several medications were prescribed by the physician, the nature of which was unknown to the parents. Under treatment with the prescribed medications the child became afebrile. However, lethargy and occasional vomiting, followed by refusal of food and liquids, developed. The medications were continued up to the day of admission. One day before admission the child began to breathe very deeply and rapidly. The physician, who was again consulted, administered penicillin, oxygen, and carbon dioxide without benefit. The child was admitted to the hospital on the fifth day of illness in an acutely ill and moderately dehydrated condition. Her respirations were 32, deep, and pauseless. The temperature was normal, the pulse 140 per minute. Apathy, general weakness, and decreased deep reflexes were present. No stiffness of the neck, back, or lower extremities was noted.

The hematocrit was 40 per cent, the total white blood count was 8,500 per cubic millimeter, with a relative neutrophilia. The initial urine specimen was alkaline, gave a positive acetone and a positive diacetic reaction. Boiling of the urine, however, revealed persistence of the diacetic acid test. Accordingly, a blood sample was taken for the salicylate level. This was found to be 300  $\mu$ g. per 100 c.c. The blood pH was 7.38; the carbon-dioxide combining power was 66 volumes per cent. Spinal fluid examination revealed 11 mononuclear cells only.

Continuous intravenous fluids consisting of sodium lactate and glucose were administered promptly. While the semistuporous condition, apathy, and general weakness persisted throughout the next thirty hours, the respirations became progressively more normal in rate and rhythm. However, shortly thereafter weakness became evident in the right lower facial muscles, the quadriceps of both legs, the extensors and flexors of the neck, and in the abdominal muscles.

The respirations, which had previously returned to an essentially normal rate and rhythm, now became irregular in depth and rate, asymmetrical in rhythm, and somewhat paradoxical in type, necessitating the use of the Drinker respirator. Very shortly thereafter, in spite of continuous oxygen therapy, cyanosis, tachycardia, and pulmonary edema developed. Death occurred on the third day of hospitalization.

DR. C. HARRISON SNYDER (Assistant Professor of Pediatrics).—The history just presented serves to remind us that for the most part even in children we must always be aware of the possibilities of two diseases in the same patient at the same time. In this case there is no question but that the child had a salicylate intoxication. The high level of the blood was potentially toxic. The question of importance is whether or not the symptoms were due entirely to salicylate intoxication and what were the predisposing factors for the development of salicylate intoxication, as compared with other persons who may have the same level in the blood without symptoms. How much salicylate did this child have?

DR. ELY.—As far as we can determine, the child had a total of 52 grains of acetylsalicylic acid in the last four days, with 45 grains being administered in the last two days prior to admission.

DR. SNYDER.—The initial positive ferric chloride test for salicylate in the urine confirmed by the salicylate concentration in the blood was of great help. The hyperventilation was the most striking finding upon admission. However, when this had subsided and the ketonuria had disappeared, evidence of paralysis of the lower extremities, back, neck, and abdomen was present. Then the question of the etiology of the paralysis became important. Salicylate has, at times, a specific effect in prolonging the prothrombin time of the blood. Hemorrhages from the nose, gums, or even bleeding into the urine and from the bowel may occur. While such was not evident clinically in this case, the possibility of hemorrhagic phenomena in the central nervous system must be considered. The initial stimulation of the respiratory mechanism by the salicylate seemed to have been replaced by a disturbance of a central nature.

DR. THOMAS E. STRAIN, JR. (Assistant Resident in Pediatrics).—Do you believe that the diaphragmatic weakness, periods of apnea, cyanosis, and tachycardia could be due to fatigue of the respiratory mechanism because of prolonged central stimulation with salicylate?

DR. SNYDER.—In acute salicylate intoxication, particularly in small children, respiratory and cardiac failure may occur, perhaps on the basis of fatigue. In the picture of generalized exhaustion I would expect to see cardiac failure with right heart congestion and pulmonary edema occurring initially and the respiratory failure occurring secondarily. Also, this child appeared to present asymmetrical differences in breathing. I do not believe I have ever seen the respiratory mechanisms tire out asymmetrically. Both sides usually show the same degree of weakness as fatigue occurs. This patient developed paradoxical respiratory activity. The weakened abdominal musculature appeared to rise and fall asynchronously with the activity with the upper thorax.



One problem that bothers me is that while this is a large dose of salicylate, approximately 1 grain per pound, it is not beyond that which we give occasionally therapeutically to older children and young adolescents. Is salicylate intoxication a manifestation of hypersensitivity to salicylate, or are there predisposing factors which condition the development of intoxication?

DR. JOHN R. TORCHELE (Research Fellow).—Salicylate intoxication occurs usually when there is a high level of the drug in the blood. The height of the level however, varies with the type of illness, the age, and other factors not clearly understood. The rapidity of development and the intensity of the metabolic ketonic acidosis that develops is great. The exact mechanism is not definitely known. It is possibly an expression of some disturbance in carbohydrate metabolism. Enzymatic systems in plants, animals, yeasts, and in rat liver and kidney slides show metabolic changes under the influence of salicylate. We must always bear in mind the nature of the illness and the duration of the illness that is present in the child who demonstrates salicylate intoxication. This child had been ill for four days, during which time fever and reduced food and water intake were evident for the most part. Starvation ketosis, gluconeogenesis, and dehydration with its associated faulty endogenous metabolite excretion, seem to play a contributing part in setting up the soil for the development of an acute intoxication. One cannot discard, however, the possibility of an idiosyncrasy to the drug. Reliable histories have been obtained in which very small doses of salicylate had been given to children who developed salicylate intoxication.

DR. LEONARD MORGANSTERN (Fellow in Pathology).—Pathologic report. A description of the pathologic changes will be confined to the central nervous system in an effort to aid in the evolution of the mechanism of the symptomatology in this case. Hemorrhage was visible grossly in several organs of the body. The gastrointestinal tract showed marked injection and hemorrhage in a few areas. The kidneys, while grossly normal, also show a few small hemorrhages into the pyramids. The central nervous system showed fairly marked changes, particularly in the spinal cord. There were areas of hemorrhage visible grossly and microscopically in the gray matter in the cord.

In addition to the presence of hemorrhage throughout the spinal cord there were specific changes in the anterior horn cells of the cord. Several stages of neuronal degeneration were present. Some cells were seen in which there was clumping of the Nissl substance. It seemed to be distributed toward the periphery of the cell. Some cells were seen in which there was further evidence of neuronal change. Chromatolysis of the cytoplasm with beginning nuclear degeneration was present. Finally, areas were seen in which glial cells surrounded pyknotic neurones, seeming to engulf them—the picture of neuronophagia. In scattered areas throughout the gray matter of the cord, small focal areas of the cellular infiltration were seen. These consisted predominantly of lymphocytes with a few polymorphonuclear cells. Early perivascular cuffing was seen in some of the blood vessels of the cord.

These pathologic changes in the central nervous system are compatible with the changes due to acute poliomyelitis. While the hemorrhagic phenomena described in the kidney, gastrointestinal tract, and spinal cord are also frequently found in poliomyelitis, one cannot say from the pathologic findings whether or not these hemorrhagic phenomena were accentuated or specifically due to the prothrombin time change which may be seen in acute salicylate intoxication.

### Case 2. Gaucher's Disease

DR. WILLIAM B. ANDERSON (Intern in Pediatrics).—We recently have had the opportunity to study Gaucher's disease in a brother and sister, ages 5 and 10 years, respectively. The boy was seen by his local physician because of complaints of anorexia and an enlargement of the abdomen which had been progressive for several months. His physician detected an enlarged spleen and referred the boy here with the tentative diagnosis of Gaucher's disease. Six months later the sister, aged 10, developed a poor appetite and her physician, upon examination, detected an enlarged spleen and referred her here. Since the course and laboratory findings in both children were essentially the same, I will present only those of the 10-year-old girl.

Physical examination revealed a pale girl with an enormously enlarged spleen. The spleen filled the entire left one-half of the abdomen and dipped into the pelvis.

Examination of the blood presented the following: The hemoglobin was 10 Gm, red blood count was 4,840,000, hematocrit was 40 per cent, the leucocyte count was 5,000, the differential count was neutrophils 56 per cent, eosinophils 3 per cent, lymphocytes 37 per cent, and monocytes 4 per cent. Bleeding time (Ivy method) and clotting time (three-tube method) were normal. The clot retraction, however, was poor. The platelet count (Rees-Ecker method) was 92,000 per cubic millimeter. Bone marrow aspiration was done and the details will be presented by Dr. Maurice Victor. A splenectomy was performed without complications. Convalescence was uneventful. Repeat bone marrow aspiration and changes in the peripheral blood were observed sequentially following splenectomy and will be discussed by Dr. Victor.

DR. DICK D. WITZEL (Assistant Resident in Pediatrics).—As Gaucher's disease is a rather unusual and infrequently encountered disease, it seemed advisable to review briefly some of the outstanding features as presented in the literature. There are two forms of Gaucher's disease described: a chronic form, which occurs in childhood and is often not diagnosed until adult life, and the acute form seen in infancy. Chronic Gaucher's disease is a rare familial disease. It is thought to be a disorder of the lipid metabolism. Clinically, the disease is characterized by splenomegaly, anemia, leucopenia, skin pigmentation, and occasionally by bone disorders. Histologically one finds in the bone marrow and spleen large Gaucher cells which are filled with an abnormal lipid, ceroid. The age is of some importance, for in one series of sixty-six cases over 50 per cent of the patients were diagnosed before the age of 8 years. The outstanding

feature in early Gaucher's disease is splenomegaly. As the condition progresses there may be enlargement of the liver. In the classical case the patient is found to have an enlargement of the liver and spleen which exceeds that seen in practically any other disease. The anemia has been described as a normocytic anemia. There is nearly always a leucopenia and a thrombocytopenia. At times a relative monocytosis is present. Hemorrhagic manifestations may occur and are thought to be due to the thrombocytopenia. In acute Gaucher's disease, hemorrhagic manifestations may be the presenting complaint. The enormous enlargement of the spleen produces only a dragging sensation and discomfort in the left upper quadrant due to its weight. Pain may be present because of an infarct in the large spleen. The bone changes are of interest: at times rarefaction and osteoporosis may be seen. Histologically this is due to the presence of Gaucher cells in the medullary cavity. Due to the expanding medullary cavity, the cortex may thin and the bone flare out at the metaphyseal ends. Roentgenologists have described the Erlenmeyer flask shape to the lower end of the femur. The acute form of the disease, which occurs in infants usually before the age of one year, deserves special attention. This is a very fulminating form and the child often presents neurological findings such as convulsions and opisthotonus, in addition to the splenomegaly. Anemia and hemorrhagic manifestations are common and the infant usually expires before the end of the first year. Diagnosis can be made only by finding the abnormal cells of Gaucher's disease in the bone marrow or spleen.

DR. W. DEAN BELNAP (Fellow in Pediatrics).—There are a few points about the etiology or the predisposing factors that deserve attention. There are two major theories as to the pathogenesis of Gaucher's disease. One theory holds that there is an injury to the storage cell itself which leads to abnormal lipid production in the cell; that is, that there is a disease of the reticulum and that these diseased reticular cells produce an abnormal lipid. This particular theory is not considered too seriously by the majority of workers. It appears to be the consensus of opinion that the defect is a general metabolic one in which storage of the abnormal lipid by the reticuloendothelial system and other blood-forming cells is a secondary phenomenon. There are, however, differences in opinion as to the nature of this metabolic defect. One worker states that the abnormal lipid is formed somewhere outside of the cell and secondarily stored within the cell. Others hold that there is an abnormal destruction of blood, and that one of the products of the blood destruction is kersin. This released kersin is then thought to be deposited in the reticulum cells. Here the presence of hemochromatosis is considered as evidence of chronic blood destruction. Likewise the thrombocytopenia and anemia are thought to be due to the disturbance of hematopoietic elements, which share in this storage process. Finally, analysis of the exact chemical nature of the kersin in Gaucher's disease has led to another theory about the disease. The observation that the kersin in Gaucher's disease contains glucose instead of galactose justifies a new hypothesis. Ordinarily, kersin contains galactose and is found in small quantities in the body. The individual with Gaucher's disease evidently produces a kersin-containing

glucose instead of galactose. Apparently, he cannot utilize this particular compound and it becomes a foreign body. Thus, the reticuloendothelial cells will store this foreign material.

These abnormal cells containing the chemically different kersin are found in largest numbers in the blood-forming organs. Apparently such disturbance is not compatible with normal red blood cell, white blood cell, and platelet production. Dr. Victor, would you comment on the blood changes found in Gaucher's disease?

DR. MAURICE VICTOR (Fellow in Hematology).—I feel that most of the changes in the blood are on the basis of hypersplenism. In Gaucher's disease there is marked enlargement of the spleen. This enlargement of the spleen is associated with a functional disorder. Thus we see early a depression of the platelets, later a depression of the white blood cells, and finally a depression of the red blood cells in the peripheral blood. We have evidence of this in these children. The brother of this patient had a thrombocytopenia and a leucopenia. Undoubtedly, if he had not been splenectomized he would have developed an anemia. The little boy, prior to operation, had a white blood cell count around 4,000 and a platelet count in the neighborhood of 70,000. We observed his blood and bone marrow subsequent to operation several times. His white blood count rose to about 14,000 and his platelet count rose to 300,000 per cubic millimeter. This little girl that has just been splenectomized will, I am sure, eventually show a rise in the white blood count. As you note, her platelet count, which was originally 90,000 per cubic millimeter, bounded right back to a normal level within a few days after the operation.

Sternal punctures were done before and after operation on both of these children. We were particularly interested in the platelet cell and the megakaryocyte. In looking at the megakaryocyte in the bone marrow before the operation in these children, we found some changes, histologically, from their usual appearance. The nucleus was fairly normal, it was well circumscribed, but the cell had no platelets around it. We counted 100 megakaryocytes and of the entire number only three or four showed some platelet production. Normally between 60 per cent and 70 per cent of the megakaryocytes observed in the bone marrow show evidence of platelet production. After operation the little girl showed a prompt return to the normal picture, as evidenced by 65 per cent to 70 per cent of the megakaryocytes in her bone marrow showing platelets around the periphery. We have seen this phenomenon several times in other conditions, such as primary thrombocytopenic purpura.

DR. JOHN A. ANDERSON.—What is your opinion regarding the specific type of cell in Gaucher's disease and its relationship to the chemical abnormality of kersin?

DR. VICTOR.—It is very difficult to read function into morphology. However, we examined the bone marrow of these children very carefully and feel that we could trace the development of these lipid-containing cells from a very early stage right up to the adult form. Most cells that had been described in the marrow are the typical large, swollen, adult cells containing the kersin. Other "immature" cells as yet free of kersin were observed.

DR. ROBERT R. MARTELLE (Assistant Resident in Pediatrics).—What about the genealogy of these children? It is my understanding that Gaucher's disease occurs predominantly in individuals of Jewish descent.

DR. VICTOR.—In the Division of Hematology we have on record seven cases altogether and there is only one family that is Jewish.

### - Case 3. Hemophilia

DR. JOSEPH R. NEWTON (Assistant Resident in Pediatrics).—We are fortunate to be able to present today two cases of hemophilia. The first patient is a 2-year-old white male child whose bleeding tendency was first noted following circumcision at 7 days of age. Since then there have been numerous bleeding episodes. His present admission was occasioned by the appearance, two days ago, of a large, tender mass in the right side of the abdomen. Coincident with the appearance of this mass, pallor and lassitude developed. Physical examination presented a temperature of 102° F., respiratory rate of 40 per minute, and a pulse rate of 160 beats per minute. Blood pressure was 88/32. He was pale, listless, and moderately obese. Numerous fresh and old ecchymotic lesions were scattered over his body. The right half of the abdomen presented a large, firm mass which extended from the thorax to the right flank and which involved the entire right side. Clinically this was felt to be a large hematoma of the abdominal wall.

Examination of the blood revealed the following findings: the hematocrit was 16 per cent; white blood count was 12,650 cells per cubic millimeter; platelet count was 180,000; bleeding time by the Ivy method was 7 minutes; clot retraction was normal. Two hours after the bleeding time was performed, the puncture wound again began to ooze and continued to do so for the next twelve hours. The child was given several small transfusions and two injections of 200 mg. each of antihemophilic globulin. Three days later his clotting time returned to normal and the hematocrit was rising.

The second child to be presented is a 3-year-old white boy. This child's bleeding tendency was first noted at the age of 6 months, when he first began crawling about. Since then he has had numerous bleeding episodes. This admission was occasioned by a bump on the head which caused a large hematoma which continued to spread until it had infiltrated the entire frontal and orbital region. Physical examination revealed the large hematoma on the face and numerous other hematomas and ecchymosis about the body. There was a swollen, painful, left elbow which suggested a hemarthrosis.

Examination of the blood revealed the following information: the hemoglobin was 10 Gm., the hematocrit 35 per cent; white blood count was 24,600; differential count was 75 per cent neutrophils and 25 per cent lymphocytes; bleeding time (Ivy method) was 6 minutes; clotting time by the three-tube method was 90 minutes; clot retraction was normal; the platelet count was 200,000 by the Rees-Ecker method.

This child received only 200 mg. of antihemophilic globulin every eight hours for three doses. He responded satisfactorily to such medication and the clotting time reduced to 43 minutes.

The family background of these two children was investigated carefully. The maternal uncle of the first child was said to be a bleeder. No family history of blood disease or hemorrhage was present in the family of the second child.

DR. JOHN A. ANDERSON.—Of the mechanisms normally concerned in hemostasis, such as retractility of the blood vessels, the components of the blood itself, the clot retractility, and certain tissue factors, which of these are important in these two patients?

DR. MAURICE VICTOR.—Interestingly enough, most of these mechanisms were illustrated in the cases presented this morning. The importance to hemostasis of blood vessel contractility was well illustrated by the first case. You recall that when a bleeding time was done a fairly normal value was obtained, but two hours later the puncture wound again began to ooze. This illustrates the fact that hemostasis in anyone, and especially in the hemophiliac, results from several factors. Perhaps the most important of these is this ability of the blood vessel to contract. This contractility of the capillary is the factor which causes cessation of bleeding as ordinarily measured by the bleeding time. Then, when the vessel again dilates after an hour or two, bleeding begins again. This child was unable to form a clot at the puncture wound.

The first case illustrated the importance of another hemostatic factor which you mentioned. The clotting time first done on blood obtained by jugular puncture was 10 minutes, a value quite within normal limits. The reason for that is undoubtedly the fact that there was a great deal of probing about and manipulation of that vein during the venapuncture. Therefore, there was enough tissue factor (thromboplastin) liberated to give that particular sample a normal clotting time. Nevertheless, that child had a very prolonged clotting time as evidenced by the fact that blood drawn with good technique failed to clot within three hours. There are several factors which can influence the *in vitro* estimation of the clotting time. One of them is this probing about the vein with a consequent liberation of tissue thromboplastin. Another is the temperature at which the test is run; the tubes should be in a water bath at 37° C. Even excessive manipulation of the syringe or agitation of the various tubes will alter the coagulation time. The importance of all these points is obvious. A normal coagulation time in a child with a clinical history of hemophilia should receive careful scrutiny regarding the technique with which the value was determined.

Another mechanism concerned in hemostasis lies in the components of the blood itself. The fundamental defect in hemophilia undoubtedly lies here.

Of the several factors in the blood which are important to the clotting mechanism, the calcium, fibrinogen, and prothrombin content are not disturbed in hemophilia. Largely by exclusion, attention has centered around a defect in the thromboplastin mechanism. As thromboplastin was thought to be in the platelets, since the number of platelets is normal in hemophilia, it has been reasoned that there must be a qualitative defect in the platelets. It was felt that perhaps the platelets were too stable and did not liberate their thromboplastin readily enough. This reasoning, however, left several questions unanswered and many investigators continued searching for the actual source of thromboplastin.

You are all familiar with the work done in Boston in isolating a substance from the plasma which can bring the prolonged clotting time of a hemophiliac back to normal. This substance is protein in nature, is found mainly in Cohn's fraction one, and to some extent in subfraction two and three, and to a very small extent in fraction four. Plasma, free of platelets, contains this factor, called the anti-hemophilic globulin, and it is now generally accepted that thromboplastin is essentially a plasma factor. The question arises, if thromboplastin is in the plasma and not in the platelets, and yet the platelets are responsible in some way for the clotting, what is it that the platelets contain that helps the clotting mechanism? Recently it has been shown that the platelets are very essential to the clotting of hemophilic blood. If a sample of hemophilic blood is divided into two portions and one portion is centrifuged at 1,000 R.P.M. and the other is centrifuged at 3,000 R.P.M., it is possible to prepare two samples of plasma, one containing platelets and the other relatively free of platelets. The clotting time on the addition of calcium chloride to these two samples is distinctly different. The hemophilic plasma free of platelets requires twice as long to form a clot as the hemophilic plasma containing platelets. Samples of normal plasma prepared in this same manner have the same calcium chloride clotting time in both platelet-free and platelet-containing samples. Further experiments have provided a fairly adequate answer. These suggest that thromboplastin is not actually in the plasma as such, but is present as an inactive precursor called thromboplastinogen. Platelets appear to contain an enzyme which is capable of converting thromboplastinogen in the plasma into thromboplastin. Many observations substantiate this. The injection of thromboplastin into the blood will cause prompt clotting. The injection of antihemophilic globulin will also reduce the clotting time. The effect of antihemophilic globulin, however, occurs slowly and clotting time is reduced over a period of twenty-four to forty-eight hours. Finally, it has been shown that the platelet is actually free of thromboplastin by demonstrating that platelet extracts fail to influence the formation of a calcium chloride clot in normal plasma. On the other hand, thromboplastin has a marked effect on calcium chloride plasma-clotting mechanism. In other words, thromboplastin as such is immediately free and active, while the thromboplastin in plasma is present in a bound or inactive form. Our defect in hemophilia in the light of this evidence is a deficiency in thromboplastinogen.

#### Case 4. Hypothyroidism

DR. WILLIAM B. ANDERSON.—The case to be presented is that of B.S., a boy, 15 years of age. According to the parents, this child had a normal developmental history, uncomplicated by illness of a serious nature until the age of about 10 years. At this time he began to complain of listlessness, easy fatigability, and vague dull pain in the extremities, particularly on walking. Dryness of the skin, lack of attentiveness in school, and a diminished tolerance to any type of vigorous activity was present. These symptoms had become most evident in the past three years. The child also stated that he very seldom perspired, even in warm weather, and that he was often cold when others in the room seemed to be comfortable. There has been a failure to gain weight, and, according to the history, a failure to grow in height.

Physical examination presented a child with a normal temperature, a pulse of 76 per minute, respirations of 24, a height of 57¼ inches, and a weight of 71 pounds. Positive findings of interest were dryness of the hair, a moderate puffiness of the upper eyelids, and a rather apathetic facial expression. The general nutrition of the body was poor, and the skin somewhat dry and scaly, particularly over the abdomen. The heart rate was heaving and slow with tones of good quality. No murmur was audible. The blood pressure was right arm 102/82; left arm 108/78. The resting recumbent pulse was found to be 68.

Laboratory examination presented the following: the blood cholesterol was 265 mg. per cent, the alkaline phosphatase, 3.6 Bodansky units; the Van den Bergh, total, 0.7 mg. per cent; plasma protein was 8 Gm. per 100 c.c. of plasma composed of albumin, 5.7 Gm., and globulin, 2.3 Gm. The hemoglobin was 12.5 Gm.; the hematocrit was 42 per cent; the erythrocyte sedimentation rate was 4 mm. in the first hour; the white blood count was 9,300 per cubic millimeter with 38 per cent segmented neutrophils, 1 per cent basophiles, 1 per cent eosinophiles, 6 per cent monocytes, and 54 per cent lymphocytes.

Electrocardiogram presented only sinus arrhythmia and ventricular extrasystoles. X-ray of the epiphyses of wrist, elbows, and crests of the ilium were interpreted as normal. The heart and lungs were normal roentgenologically.

The basal heat production was found to be 49.0 calories per hour. Child Research Council standards for comparison are as follows: calories per square meter per hour, 47.38; calories per hour related to weight, 49; calories per hour related to height, 50.7.

DR. JOHN A. ANDERSON.—This child was presented to emphasize the importance of evaluating the longitudinal growth process of the child as an aid to clinical diagnosis. While subjective symptoms are present in the history, such as listlessness, easy fatigability, dryness of the skin, and diminished tolerance to cold, they are, however, only a suggestion of hypofunction of the thyroid. When the growth and developmental pattern in this child is considered with them, they become important symptoms. Superficial examination of the child does not reveal any of the striking characteristic findings that are seen in the hypothyroid child, such as the puffiness of the eyes and face, the presence of supra- and infraclavicular fat deposits, the dry sparseness of the hair, or the dryness of the skin. He looks like a boy who is rather tired, indifferent to his surroundings, suffering from a moderate degree of malnutrition, and smaller than the average for 15 years of age, but still could be considered in the lower zone of average. In spite of his general appearance of fatigue and poor nutrition the child ate well, and it was a puzzle to the parents that he could eat so well with such a good appetite and still fail to gain or grow. We also note that there is some slight delay in the onset of puberty. He is at the stage characterized by beginning enlargement of the penis and testes and the presence of a few hairs on the mons pubis.

Fortunately the mother was able to bring in a record of his developmental progress as recorded at the time of visits to the physician and at the school health examination. We were thus able to construct the developmental progress of this child from the age of 6 to the present age of 15 years. These have been plotted



on the Wetzel Grid and it will be noted in the first slide (Fig. 1) that for the period of 6, 7, and 8 years, this child stayed essentially in the M channel and attained, by 8 years of age, seventy developmental units, an essentially average achievement. However, at the age of 11 years, at which time he began to have symptoms, we note that he had shifted over to the B<sub>2</sub> channel and now was in the 82 per cent auxidrome developmental zone. Subsequent to this, we note progressive failure in his development, so that he is now, at 15 years of age, in the B<sub>-3</sub> channel, and is well below the 98 per cent auxidrome developmental zone.

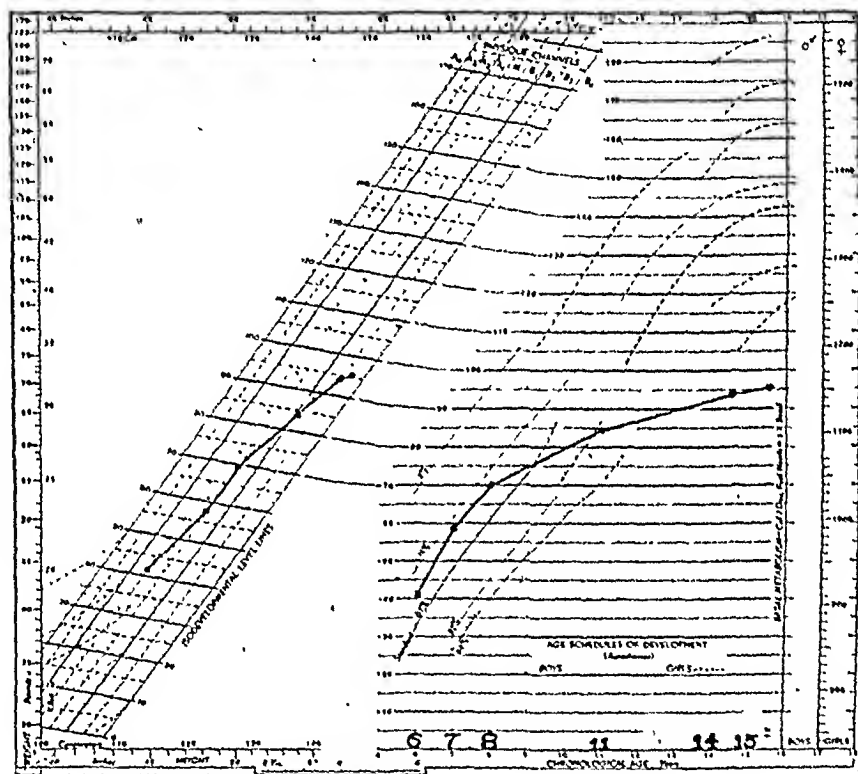


Fig. 1.—Growth curves as plotted on the Wetzel Grid for B. S.

I believe it is important to emphasize one other point, and that is that there has been progressive failure with each year since 10 years of age. The child began to fail in his developmental progress between the ages of 8 and 11 years. However, the degree of failure in this period was not as great as it was between the ages of 11 and 14 years. Within the last year his developmental achievement has been negligible. I believe that this is an important point which aids in our diagnosis. The deficiency disease is expressing itself with increasing intensity as the child grows older.

DR. WESLEY ANDERSON of OGDEN, UTAH (Visiting clinical instructor in Pediatrics).—What about the significance of the alkaline phosphatase, cholesterol, and the basal metabolic rate in this case?

DR. JOHN A. ANDERSON.—I believe that the alkaline phosphatase value of 3.6 Bodansky units as well as the cholesterol of 264 mg. per cent help us considerably. These values are not strikingly abnormal, but certainly are beyond the range which may be considered average for children of this age. It is difficult, however, to explain the apparent normal basal energy production in this child. One must first ask the question, What was the basic energy production of this child at the age of 6, 7, and 8 years, and what position did he occupy in relation to other children? This "normal" value for heat production may be low for him. It is entirely possible that his basal calorie production was previously in the upper percentile of average children. It is entirely possible that if he responds well to thyroid medication, it may be necessary to maintain him in the upper zone of average for heat production in order to insure proper functions of all systems. In other words, all children do not fall exactly on the zero or midzone line. He could be essentially normal at a basal metabolic rate of plus 18, and could show hypothyroid symptomatology and physiologic effect now with a basal metabolic rate which is near the zero zone. I think this serves to emphasize that the basal metabolic rate alone is of very little value in aiding in the diagnosis of hypothyroid states. It is only one factor which must be correlated with the over-all picture.

Obviously, at this age x-rays of the epiphyses did not help. The hypothyroidism was beginning to express itself between the ages of 10 and 11 years when the epiphyses were already formed, thus no significant influence on the epiphyseal development became evident. Roentgenograms of the epiphyses of the elbow for evidence of fusion were not of any help.

To emphasize the importance of evaluating the growth progress of the child, the following case is one in which growth failure also occurred. Here, however, it expressed itself in a different manner.

E. T. was first seen at the age of 10 years, complaining of pain in his hips on walking, constipation, and slow growth. The child was doing well in school and kept up with his grade. The earliest history dates to about the age of 2 years, when, the mother stated, he was an unusually fat and healthy child, but was, however, shorter and more stocky than any of her other children were at that age. Since about the age of 2 years, no real problem existed except definite evidence of slow growth which became most striking at about the age of 6 years. Between the ages of 6 and 10 years, the child failed to grow more than one inch. The chief concern was the constipation. The child's abdomen was large, doughy, and protuberant. The bowels moved about once a week. Physical examination on admission revealed a child of a short, dumpy stature; the hair had good color and was not dry or sparse; there was a moderate fullness of the face, the trunk was relatively thick, and the large, protuberant abdomen was evident. Excessive dryness and sealiness of the skin were not present. Laboratory examination revealed a moderate anemia, a hypercholesterolemia, and a basal metabolic rate of minus 26 (Boothby-Sandford Standards). Three carpal centers were present in the wrist roentgenologically. We were able to obtain the growth record of this child since the age of 7 years, at which time he attended school. These have been plotted on the Wetzel Grid for comparison with an essentially average

child who is superior in his height and weight progress (Fig. 2). It is of interest to note that here is a child who presents progressive developmental failure quite differently expressed than that of the first child. This child, when first measured for height and weight at the age of 7 years, was below the 98 per cent auxidrome. He had achieved only twenty developmental units by the age of 7 years, when he should have achieved at least thirty-five developmental units.

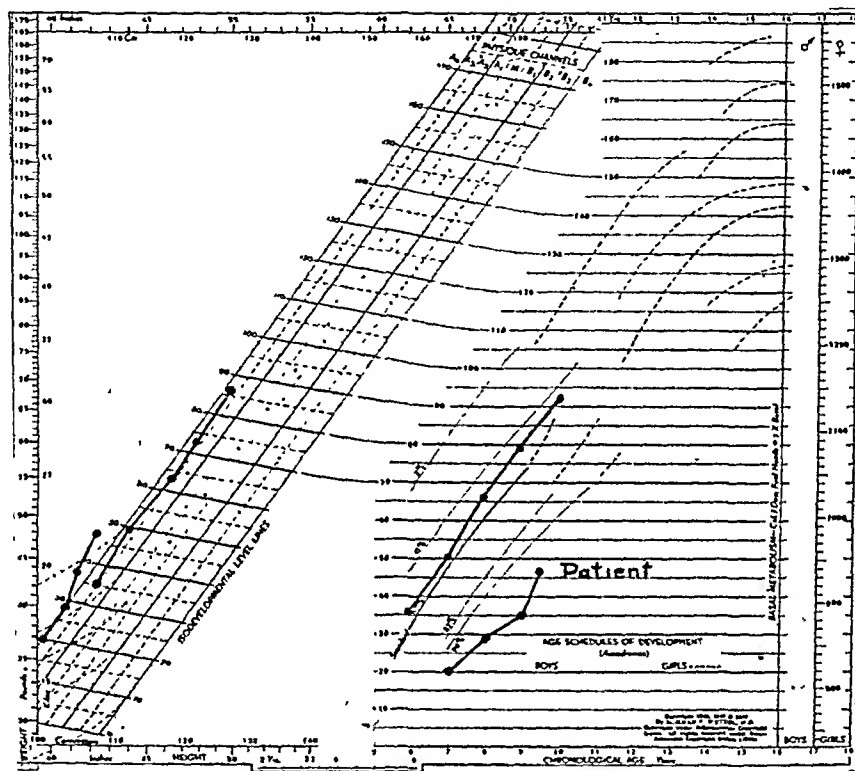


Fig. 2.—Growth curves of E. T. as compared with a normal boy of the same age and plotted on the Wetzel Grid.

However, instead of leaving the A<sub>4</sub> physique channel and crossing into a lower channel, the boy became progressively stockier and heavier, so that now he is further beyond the A<sub>4</sub> channel than indicated by the first height and weight at 7 years of age. I imagine that if we had been able to obtain height and weight records from birth on, we would have seen a progressively increasing rate of failure in his developmental progress at the time the hypothyroidism was just beginning to express itself clinically, perhaps around the age of 2 years. The curves that we are looking at now are, perhaps, only the consistent slow increment in development that the hypothyroid may show after the hypofunction has expressed itself completely.

DR. WESLEY ANDERSON.—I have found in my private practice that hypothyroidism is more frequently found in boys in the prepuberty age than it is in

girls of this age. We have been brought to believe that hyperthyroidism is more frequent in prepuberal girls and hypothyroidism is more frequent in postpuberal girls. In any event, I think we should be alert to the diagnosis of hypothyroidism in boys, perhaps almost as frequently as in girls.

DR. C. HARRISON SNYDER.—Is there anything here that offers information as to whether or not this is a specific failure of the thyroid gland, or whether it is due to a specific deficiency in the thyrotropic hormone of the pituitary?

DR. JOHN A. ANDERSON.—I do not believe we have anything in our laboratory or clinical evaluation which will permit us to differentiate between these two etiological factors. Pituitary thyrotropic hormone assay has not been done. As yet, no associated pituitary hypofunction syndrome has presented itself, such as a deficiency of parathyrotropic, adrenotropic, or gonadotropic hormones. A disorder in one or more of these systems may express itself following therapy with thyroid. I believe we will have to wait for a matter of months under thyroid therapy in order to be certain that we are dealing with a specific thyroid gland failure.

DR. SNYDER.—One of these boys got fat as he was developing his hypothyroidism and the other one got thin. How do you explain these differences?

DR. JOHN A. ANDERSON.—No specific tests were done to explain the reason for obesity in the one child as compared with the failure of fat deposition in the other. However, when we realize that hypothyroidism may be associated with faulty fat absorption and faulty absorption of the fat-soluble vitamins such as vitamin A and D, I do not believe that we are stretching the point too far when we state that the defective fat absorption mechanism expressed itself earlier and more severely in the one child as compared with the other. There certainly must be differences in the way individuals as a whole respond to an inadequacy. It is also possible that there are differences in the manner in which respective organ-systems respond. It will be interesting to see whether the first child will gain weight on the administration of thyroid, and I assume that he will, while the other child has been observed sufficiently long to know that he lost his obesity but gained in height and muscle mass.

#### Case 5. Foreign Body in Bronchi

DR. THOMAS E. STRAIN, JR.—N. K. is a 2-year-old white female infant who was well until two days prior to admission. At that time, while eating peanuts, she seemed to strangle, became red in the face, and coughed considerably for a moment. The cough gradually subsided during that same afternoon and the child spent a restful evening and night. However, the following morning noisy, wheezing respirations developed, which were accompanied by an intermittent expiratory grunt and some pain in the chest. That evening the patient was seen by the local physician, who made a presumptive diagnosis of peanut aspiration and referred her to this hospital. Examination upon admission, thirty-two hours after the aspiration of the peanut, revealed a temperature of 101° F., a pulse of 132 per minute, and a respiratory rate of 26 per

minute. Physical findings of importance were limited to the respiratory system. Auscultation and percussion of the chest revealed no abnormality except for some sibilant and sonorous râles which were heard over both hilar regions posteriorly. Throughout the night the child was placed on penicillin, sulfadiazine, and placed in the crib under a steam tent with the head in a dependent position. By the following morning the physical examination revealed that the breath sounds in the right lung fields had diminished relative to the breath sounds in the left lung field. Shortly thereafter the percussion note over the right lower lobe anteriorly became tympanitic. Roentgenograms and fluoroscopic examination now presented evidence of an obstructive foreign body in the right main bronchus. The child was bronchoscoped immediately thereafter, and one-half of a peanut was removed from the right lower lobe bronchus. The chest findings reverted promptly to normal thereafter.

DR. RALPH RIGBY (Assistant Clinical Professor of Surgery, Laryngologist).—This child presents a not unusual and fairly classical picture for a foreign body in a large bronchus. There are certain things, however, that one should keep in mind. First, if someone is there to observe the incident, there is usually a definite set of symptoms referable to the respiratory tract immediately following the aspiration of a foreign body. This child gagged, became red in the face, and had difficulty in breathing for only a few seconds. She coughed for a short while and then the cough subsided. Next, the child exhibited a "symptomless interval," during which time the patient did not appear ill and did not show anything of diagnostic importance upon examination at the time of admission to the hospital. This interval is not truly symptomless, as careful auscultation may reveal a "click" or a transitory wheeze on inspiration or expiration. Finally, we approach the stage which can be considered the stage of complications. The manner in which these complications may express themselves is dependent upon the type of foreign body, its location in the bronchial tree, and whether or not there is a partial or a complete obstruction of one or more bronchi. The history in this child followed a characteristic pattern, and suspicion that the foreign body was still present at the time of admission arose because of the sibilant wheeze heard posteriorly by one of the early examiners. Percussion and auscultation signs were also negative at this time and it is doubtful whether or not fluoroscopic or roentgenologic inspiration and expiration films would have been of real value. However, by the next morning the physical findings had changed definitely. Now, a tympanitic percussion note and *decreased breath sounds* were obtained on the right side. This is characteristic of the ball-valve type of emphysema due to a partial obstruction of a large main bronchus. Peanuts nearly always cause the initial obstructive emphysematous picture. However, if we had not seen this child for four or five days, there would have been a reaction of the bronchial wall to the peanut, and then instead of the obstructive emphysema she would have developed a complete obstruction and an atelectasis of the involved segment.

There is another point in this child that is of some importance. It was stated that she had a fever on admission. An examination of the nasopharynx at the time presented evidence of a mild upper respiratory infection. It is not

uncommon to find mild upper respiratory infections in children who aspirate foreign bodies. The exact etiological significance of this is not known, but I am inclined to believe that the swelling of oropharyngeal tissues, the congestion of the nose, and the presence of mucus and mucopurulent discharges in the oral pharynx must play an important part in permitting the aspiration of foreign bodies. This point should be borne in mind in the examination of every child who has a foreign body in order to determine whether or not the febrile response that is present is due to the consequence of the foreign body in the lungs or was pre-existent to the aspiration of the foreign body.

DR. JOHN A. ANDERSON.—The inspiration and expiration films were attempted in this child without success. This procedure did not offer much of diagnostic importance regarding localization. Fluoroscopy, however, appears to me to be a most important procedure to confirm the physical signs that are observed by percussio and auscultation. It seems to be a good principle that the presence of any localized whistle or wheeze or click within the chest should lead to fairly prompt fluoroscopy. What about this "symptomless interval"? How long may it go on?

DR. RIGBY.—The "symptomless interval" may go on almost indefinitely. It depends upon the type of foreign body aspirated. Candied foreign bodies are very irritating to the bronchial mucous membranes. Other foreign bodies are slightly irritating. I have removed foreign bodies from the lungs that had been there, according to the history, for as long as forty-two years without producing significant symptoms in the interval. In my experience, the age of the child sometimes helps to identify the nature of the foreign body. That is, we find peanuts most frequently in children between the ages of one year and 1½ years, coins from 1½ to 4 years, and open safety pins from 3 to 10 months of age.

DR. O. L. ROSS (Assistant Clinical Professor of Pediatrics).—I would like to relate a history on a child in which the so-called "symptomless interval" was periodic in nature for a period of about three to four weeks. This was a 16-month-old child in whom the history of a foreign body aspiration was not available. The chief complaint was dyspnea and cyanosis. He had been observed by his private physician for a period of three weeks because he had had "colds" off and on during this period. There would be an attack characterized by fever, cough, and dyspnea which would last for several days and then clear up. These episodes had occurred three or four times in this period in spite of medication. When I saw the child he was running a septic temperature and examination revealed a complete absence of breath sounds over his left lung field. The heart, however, was shifted to the left and it was our impression that we were dealing with a pneumonia and possibly an empyema in the pleural cavity. Because of the shift of the heart to the left and the marked density observed roentgenologically over the left lung, the possibility of an atelectasis due to a foreign body complicated by pneumonia and empyema was considered. Accordingly a thoracentesis revealed a small amount of serosanguinous material obtained from the sixth interspace at the posterior axillary line. The failure to find pus and the presence of the serosanguinous fluid suggest an atelectatic lung which led to prompt bronchoscopy.

DR. RIGBY.—Here is a child who had most likely gone through the first two phases of his symptomatology following the aspiration of a foreign body. No one was there to observe the initial respiratory distress at the time he aspirated the foreign body. The periodic episodes may have been due to shifting of the foreign body, permitting re-expansion of the lung. Finally, however, complete obstruction occurred, and the third phase of symptomatology occurred. Complete obstructive atelectasis developed, during which time the air was absorbed, the lungs filled up with fluid and became secondarily infected, producing a septic course. What we have, therefore, by physical and roentgenologic examination, is a "drowned lung." The presence of the serosanguinous fluid in the pleural space is quite characteristic. I bronchoscoped this child and we got out a portion of walnut meat from the left main bronchus. Within fifteen minutes after the removal of the foreign body, the lung became moderately well aerated; however, considerable rhonchi were still present. The child has shown continued improvement and we believe the remaining lung findings are on the basis of the atelectatic pneumonia, which is likely to clear up completely.

DR. JOSEPH R. NEWTON.—Are peanuts any more likely than other objects to go farther down the tracheal-bronchial tree?

DR. RIGBY.—Any foreign body in the lung progresses as far as it can go by ratchet action. The bronchi enlarge during inspiration and decrease in size during expiration. The foreign body, therefore, goes down a certain distance, the bronchi constrict upon it during expiration, and during the next inspiration the bronchus dilates and the foreign body goes farther down. Common pins and things of a pointed and sharp nature which are not sufficiently large enough to obstruct may go down through the lungs and even below the level of the diaphragm and appear to be in the stomach.

Obviously, this last case serves to emphasize the importance of early diagnosis of the foreign body. In the adult, the early history can nearly always be obtained. However, such is not true in the child and it is necessary for the physician, when confronted with a puzzling respiratory picture, to think of a foreign body as a possibility. An effort to reconstruct the pathogenesis may then provide a pattern of events which will lead to bronchoscopy examination.

# Psychologic Aspects of Pediatrics

## ENURESIS IN CHILDREN

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FEW conditions are so troublesome and at the same time so widespread as bed-wetting in children. Opinions as to etiology are numerous and widely divergent and the literature is voluminous. Objective observations are, however, relatively few and have originated principally with the urologists.

By enuresis is meant the repeated involuntary discharge of urine after the third year of life. The time when children acquire bladder control varies widely and the choice of the third birthday as the dividing line between normality and enuresis is arbitrary. Gesell and Hg<sup>1</sup> found that the majority of children at 3 years of age are consistently dry in the morning without being picked up. Anderson<sup>2</sup> places the average age of nocturnal bladder control among children of intelligent and educated parents at 23 months. In Despert's<sup>3</sup> group of sixty children, day control was achieved on the average at 21.4 months and night control at 27.3 months of age.

Enuresis is to be distinguished from the urinary incontinence due to gross organic lesions. Involuntary micturition may be associated with local conditions in the genitourinary tract such as cystitis or vesical calculus. Under these circumstances there is marked frequency and urgency, and leucocytes or red blood cells or both are found in the urine. The etiologic significance of conditions like balanitis, phimosis, and adherent prepuce is doubtful, and cures following the correction of such difficulties are attributable to a psychic rather than a physical influence.

Urinary incontinence may be a symptom of disease of the innervation of the bladder, e.g., hematomyelia, transverse myelitis, spina bifida, or cord tumor. The association between spina bifida, bladder disturbances, and clubfoot has long been known. Enuresis may be part of a general disorder such as diabetes mellitus, epilepsy, or diabetes insipidus.

### INCIDENCE

According to a survey of 1,000 unselected children between the ages of 4 and 12 years, inclusive, in the Children's Out-Patient Department of Bellevue Hospital, 26 per cent wet themselves during the night or day or both. This includes children in whom the basis was grossly organic but such children constitute only a small proportion of the cases. It was the custom for some years in the Out-Patient Department at Bellevue Hospital to inquire about this symptom routinely and, therefore, its presence or absence was regularly noted even when the parent might otherwise neglect to mention it.

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The high incidence in the Bellevue Hospital series certainly is not representative of the general population and is due to special sociologic conditions. The figures, nevertheless, give some measure of the frequency of this condition and indicate that it is one of the most common disorders of childhood. Addis<sup>4</sup> found that 18 per cent of children had nocturnal enuresis. Her data were compiled from six Child Guidance Clinics. In Despert's<sup>3</sup> group of sixty unselected nursery school children, fourteen (23 per cent) were incontinent. Of 1,000 selectees for the draft, Thorne<sup>5</sup> found that 16 per cent wet the bed after the age of 5 years.

#### SYMPTOMATOLOGY

In most children with enuresis bladder control at night has never been achieved and nocturnal incontinence has continued from infancy. Sometimes the parents state that wetting started later on. In such instances it usually will be found that the child had been picked up previously or that he had awakened by himself and gone to the toilet or that he had actually wet himself formerly but less frequently. Wetting generally occurs every night and usually once or twice a night. A dry bed for more than a few nights is uncommon. Some children wet within an hour after being put to sleep; in others wetting does not take place until the early hours of the morning. Children rarely awake after wetting the bed. The amount of urine passed at night is large.

Friedell<sup>6</sup> made the interesting observation that in a certain proportion of children with enuresis the specific gravity of the urine is lower during the night than during the day, a reversal of the condition in normal individuals. These children were especially resistant to suggestive therapy.

Urgency and frequency during the day are present in the large majority of enuretics. They are highly sensitive to stimuli like cold, damp weather, and excitement, which increase bladder irritability in normal individuals.

Diurnal enuresis frequently accompanies nocturnal enuresis. It was present in 40 per cent of the cases at Bellevue Hospital and other observers have noted a similarly high proportion of day wetting among enuretics.<sup>7</sup>

Diurnal enuresis without bed-wetting is unusual, constituting only about 5 per cent of the patients.<sup>7</sup> It is seen in shy children who are ashamed to ask permission to leave the classroom and in children who are not permitted to leave the classroom to go to the toilet. In boys it may be due to unwillingness to take time off from play to empty the bladder. These children do not wet the bed at night because they get up out of bed to empty their bladders. Diurnal enuresis without night wetting occasionally occurs with laughter or fright.

Most children outgrow their difficulty by 12 to 16 years of age and can sleep through the night without emptying the bladder, but a considerable number continue to wet the bed in adult life. Some have nocturia without enuresis and almost all retain a "sensitive" bladder throughout life.

Enuresis nocturna, i.e., involuntary bed-wetting, is to be distinguished from voluntary bed-wetting, or factitious enuresis. This is usually psychogenic in origin. Factitious enuresis may occur if the child is too lazy to leave the bed or is afraid of the dark, if the bedroom is too cold, if the toilet is inaccessible, or in a neglected household where habits of cleanliness are poorly developed. It is

not infrequently seen in young children following the birth of a sibling. The child often wets while he is sitting on the mother's lap. In these cases wetting is associated with other "infantile reversions" such as soiling, clinging and whining behavior, demands to suck at the mother's breast or from a bottle, demands to wear diapers, etc. The wetting is temporary unless there is a basis in the "irritable bladder."

The reaction of the enuretic child toward his symptom varies considerably. Some children appear unconcerned, others assume an attitude of bravado, most are ashamed. Kanner<sup>8</sup> reports a general immaturity in the majority of his patients. In addition, he describes a host of other personality patterns, the most common of which is the whining, complaining, moody, grouchy, irritable type. Next in frequency is the restless, hyperactive, fidgety, easily excited type.

Although enuresis occurs frequently in all socioeconomic groups, it is more common in clinics than in private patients. This is due to less intensive training procedures among clinic patients, lower standards of cleanliness, inaccessible toilets, crowded quarters, making it necessary for several children to sleep in one bed, and exposure to cold and dampness. It is of interest in this connection that enuresis was a frequent complaint among soldiers in all the armies during World War I but was practically nonexistent among officers.

*Age.*—In the Bellevue Hospital series the percentage incidence of enuresis remained unchanged from the fourth through the twelfth year. Other studies<sup>9</sup> show a steadily decreasing incidence as age increases.

*Sex.*—The condition is said to be more common in male than in female children, although the opposite has also been reported. No sex difference was noted in the Bellevue Hospital series.

*Race.*—According to Davison,<sup>10</sup> enuresis is more common among white than among Negro children. He feels that this is not because of disregard of the symptom in the Negro families, since, among the poorer classes in Baltimore, Negro children are usually better cared for than white children. He attributes the difference to the greater frequency of neurotic and neuropathic conditions among whites. Anderson<sup>2</sup> found no racial difference in the incidence of enuresis. Depth of sleep has no relation to the etiology of enuresis. Enuresis is not infrequently observed in children previously continent, following a severe illness. In these patients the symptom may be based on the child's desire to retain the special attention of the parents and attendants which he had during the illness. Usually a careful history will elicit the fact that the child has had urinary symptoms such as frequency, urgency, and occasional wetting prior to the illness, indicating that the psychologic is not the only factor.

The drinking of large amounts of water before bedtime may lead to bed-wetting. Water drinking is considered a great sport by many children, and water drinking contents are engaged in with zest. This may be developed to such a degree as to lead to a diagnosis of diabetes insipidus.

Urinary acidity plays no part in the etiology of enuresis. Spina bifida occulta, as indicated by defects in the lumbar and sacral vertebrae, is no more common in children with enuresis than in those without it.

*Heredity.*—In the large majority of cases it is possible to obtain a history of urinary symptoms in one or more siblings or in the parents. Urgency, frequency, and nocturia are common complaints among the parents of enuretics.

*Mental Deficiency.*—There is no relation between enuresis and moderate degrees of mental deficiency. Children who are moderately retarded are readily trainable at about the same age as normal children. Addis<sup>4</sup> and Ackerson<sup>9</sup> found no striking difference in the intelligence quotient between enuretic and non-enuretic children. Enuresis is the rule in low-grade, mentally defective children who are incapable of learning vesical control.

*Institutional Enuresis.*—Enuresis is a major problem in institutions for the care of children but it is not clear whether it is more common there than in the home. According to A. F. Payne,<sup>\*</sup> about 10 per cent of the children at the Hebrew Orphan Asylum, New York, are bed-wetters. Payne has used many methods of treatment without success. The giving of rewards, an appeal to a sense of decency and cleanliness, isolation, and restriction of privileges were unsuccessful. Awakening the children during the night made them irritable and nervous. The most effective method used was a thorough explanation of the situation to the entire group of the children in the home in a kindly, sympathetic way.

*Electroencephalogram.*—Michaels and Seeunda<sup>11</sup> studied the electroencephalographic tracings of a group of children with various "neurotic" traits. Of all the children examined, those with enuresis had the highest association with an abnormal electroencephalogram. The commonest abnormal finding was a "wave of slow rate."

#### PATHOGENESIS

Of the numerous theories which have been proposed to explain the pathogenesis of enuresis, there are four which merit serious consideration:

1. *The urologic viewpoint:* In general, urologists hold with the early students of this subject that enuresis is due to anatomic defects in the urinary tract. They base their opinion on visualization studies of the bladder and urethra.

In a urologic study of 330 patients with enuresis resistant to ordinary methods of treatment, Campbell<sup>12</sup> found that about two-thirds showed abnormalities in the urogenital tract which he believed to be causally related to the enuresis. The most common lesion in girls was a urethrotrigonitis, the most common lesion in boys congenital obstruction along the urethra, usually at the meatus. Next in frequency in boys was a prostatitis and verumontanitis. In addition a wide variety of other lesions was found.

More recently, Cohen<sup>13</sup> described the results of a urologic study of twenty-five consecutive, unselected adult men with enuresis. Two of these had inflammatory lesions which were easily cured, resulting in a disappearance of the enuresis. Of the remaining twenty-three, twenty showed anatomic changes in the lower urinary tract. Foreshortening of the trigone (the area between the openings of the ureters into the bladder and the internal urethral orifice) was the most common finding and was observed in fourteen patients. This condition was found only twice in the course of routine cystoscopy for other conditions.

\*Loc. cit.

Neither of the patients was enuretic at the time but both had been bed-wetters until the ages of 15 and 16 years, respectively. Thirteen patients showed hypertrophy of the verumontanum without inflammatory change. Another common finding (eleven cases) was elevation of the inferior margin of the internal urethral orifice. An excavation or depression between the internal urethral orifice and the proximal end of the verumontanum was observed in ten patients. Interesting were the cystometric measurements. The curves following the injection of fluid into the bladder were normal. However, when the point of discomfort was reached and the patient was asked to exert maximum voluntary detrusor action, the pressure did not rise above 45 cm. of water (normal pressure, 70 to 80 cm.). This phenomenon, exhibited by six patients, was interpreted as indicating that sensation was unimpaired but motor power was diminished.

Organic changes in the bladder and urethra have also been found by Stockwell and Smith<sup>14</sup> in 13 per cent of a consecutive series of enuretics and by Brodny and Robins.<sup>15</sup>

Urologists agree that cystoscopic examination is indicated in enuretics who are resistant to ordinary methods of treatment. They claim that the manipulations, when properly conducted, need not be traumatic physically or emotionally.

2. *Enuresis as an undesirable habit, the result of improper training:* Holt and Howland<sup>16</sup> believed that enuresis is, in most instances, "purely a habit, often associated with other habits which indicate an unstable or highly susceptible nervous system," and they advocated intensive training procedures. This attitude represented a departure from the organic viewpoint and has received wide acceptance by pediatricians.

Their viewpoint was elaborated by Wooley,<sup>17</sup> who held that enuresis is primarily a problem of habit training and of the mental attitude of the child. Her view was that the most common failures in developing correct habits about the use of the toilet have to do with the age at which training is undertaken and with the emotional atmosphere that surrounds the training situation. She listed the errors as postponing the period of training beyond the natural time for it; conducting the training in a spirit which rouses the child's antagonism and favors wetting to annoy the parents and get his own way; making the habit of wetting an occasion for emotional scenes which permit the child to win the center of the stage and so become the object of much emotional solicitude; using methods which instill fear. Failure may also be due to excessive emotional dependence on the mother and a vague desire to continue the period of infancy. The treatment advocated consists of the elimination of improper training procedures and the introduction of proper ones.

Although improper attitudes toward toilet training are not often, in our opinion, of primary importance in the pathogenesis of enuresis, they contribute greatly to its frequency. Enuresis occurs more commonly in the poorer socioeconomic groups where toilet training is likely to be taken as a matter of course and where, consequently, tension about the toilet situation is likely to be at a minimum. Under these circumstances the normal child acquires control easily. This easygoing method is, unfortunately, not so effective in the child with the irritable bladder. Here the more systematic methods, commonly applied in the

better-off families, are more effective. There is an analogy to specific reading disability: The general run of children learn to read more quickly and easily by the "sight" method than by the older "phonic" or ABC method. Not so the child with a reading disability. He requires training in the details of his letters before he can begin to read words and he finds himself at a loss when exposed to the "sight" method.

Inadequate training procedures do not in themselves lead to enuresis in any considerable proportion of cases. Rather, intensive training serves to prevent enuresis in a certain number of susceptibles. These children do not wet the bed but they have urgency and frequency and, in many instances, nocturia.

3. *The psychiatric school:* According to this approach, enuresis is looked upon as a disorder of the personality. It is but one manifestation of a general disturbance of behavior. Beverly<sup>18</sup> describes enuretic children as infantile, finding growing up and taking responsibility too difficult. The children are timid and most of the parents describe them as nervous. Infantile habits like thumb-sucking, temper-tantrums, nailbiting, frequent crying, baby-talk are common. There is loss of a sense of security and self-confidence. Jealousy is a common finding.

In many cases the mechanism is more deep-seated. Beverly agrees with Hamill<sup>19</sup> that these children can stop wetting when they want to.

The treatment recommended consists of making the child responsible for himself, psychotherapy, and adjustment of environmental difficulties. With this regimen, Beverly was able to cure one-third of the patients and improve another third. The remainder were either unimproved or did not return. Anderson<sup>2</sup> concluded, from his own observations and an extensive review of the literature, that emotional factors constitute by far the largest group of elements in the causation or, at least, the continuance of enuresis. Infantile traits are common among enuretic children, who are timid and overly sensitive, and many of whom are nail biters. A frequent reaction is a feeling of inferiority. Habit training is one of the most important things to be considered as responsible for persistent enuresis. Gerard<sup>20</sup> found that sixty-one out of sixty-five children with enuresis presented definite neurotic patterns of which wetting represented one symptom in the syndrome. Etiologic factors of an emotional nature were found in the majority of cases. In a certain number the onset of wetting coincided with the arrival of a sibling and was part of generally regressive behavior such as whining, clinging to the mother, hostile attacks on the baby. In others it was part of general stubborn and aggressive behavior. In some instances the mothers were dominating rejectors. One child developed enuresis following the death of his father, of whom he was very fond.

In a group of enuretics who had been either analyzed or studied fairly intensively, Gerard found that the boys were passive, retiring, and self-deprecatory. They avoided rough boys' games for fear of injury. They were slow and dawdling, constantly sought help and assurance in performing the usual tasks, and indulged in evasive petty lying. At school they were inattentive and distractable and did poor work. At times they clowned. The girls were more

normal in their behavior. They were active, often leaders, and they were independent and proficient in performing tasks. They did good work at school and behaved well. They were strongly competitive in play, especially with boys. Though they were fearless in day activities they shared a common anxiety with boys, that of nocturnal fears, and they often had nightmares. Gerard concludes that the boys disclosed material indicating a fear of women as dangerous persons who could injure or destroy them if they themselves were active. The mechanism of overcoming this fear was an identification with the woman in the form of a passive attitude and an avoidance of the active role of the male. Urination was conceived of as a passive act for which the child has no responsibility. The girls, on the other hand, presented material which expressed, clearly, fear of man as a destructive aggressor. They avoided this difficulty by identifying themselves with the active male rather than the passive female. Enuresis in the girl represented an active destructive process rather than a passive flow as it did in boys. In both boys and girls fear of harm from persons of the opposite sex was the principal factor. This fear arose from destructive wishes toward the rival parent, traumatic sex experiences or information, and experiences of parental rejection or seduction.

It is difficult to evaluate the psychiatric viewpoint, since one cannot readily distinguish emotional disturbances which are etiologically related to the symptom from those which result from the reactions of parents, playmates, school personnel, and the child himself to the symptom. Moreover, enuresis being so common, it will often be present in neurotic children and will then be used by them as part of their neurosis. Adherents to the psychiatric viewpoint rely for treatment on psychotherapy. To the extent that they try to correct faulty attitudes in the parents and to instill confidence in the child their approach is, without question, beneficial. But favorable results alone can hardly be used as proof of their thesis. Enuresis has been cured by a host of unrelated remedies which can have no relation to the etiology of the condition. It has been said that the physician's conviction of the efficacy of his own particular method of treatment is the most important factor in the cure of enuresis.

4. With full recognition of the importance of other contributing factors, we here propose a fourth approach to the pathogenesis of enuresis. Two features stand out prominently in the histories of children with enuresis, the primary importance of urgency and the familial nature of the affection. A third interesting feature is the persistence of a "sensitive" bladder throughout life.

Urgency, associated with frequency, has been referred to as pollakiuria or the "irritable bladder."<sup>21</sup> It is present in the large majority of enuretics. It may be unaccompanied by enuresis, or involuntary micturition may occur only occasionally during periods of nervous tension, cold weather, or when a toilet is inaccessible. Indeed pollakiuria without enuresis is often seen in well-cared-for, intelligent children. These potential or latent bed-wetters are frequently found in the families of enuretics. It is reasonable to assume that the intensity of the defect varies as do other biologic attributes. Such children are difficult to train and they may be 4 or 5 years old before complete urinary control is established. Gesell and Ilg<sup>22</sup> speak of "a group of cases in which the slowness

in training is due to specific retardation. These children are intelligent and well-constituted emotionally yet they are backward and inept in sphincter control. It is almost as though they were handicapped by a specific disability (like constitutional poor spelling). The difficulties so transparently have a developmental origin that they should be guided on that basis." There is reason to believe that the abnormality in urinary control is already present in infancy. It may be suspected in this age group when repeated episodes of ammoniaecal dermatitis occur or when the diaper rash is unusually persistent. In such infants urinary frequency is often present while the ammoniaecal dermatitis is present and persists after the condition has been alleviated. Inquiry will often reveal a history of urinary difficulties in a parent or the siblings.

Pollakiuria is observed in dogs, some being very resistant to training. Veterinarians differ in their interpretations of this phenomenon, one group holding that these dogs are "nervous," another group being of the opinion that the dogs are so constituted that they find difficulty in retaining their urine. It is said that dogs wet occasionally, out of spite. This may happen when a dog is left alone for a long time by his master and he then wets indoors when his master returns. Difficult trainability is seen in some litters and here again interpretations vary, one group holding that this is imitative, the other group believing that the defect is hereditary.

The second prominent feature of enuresis is its familial character. In the large majority of cases one or both of the parents has or has had urinary symptoms. Adults are often reluctant to admit that they have been bed-wetters during childhood but a history of urgency and frequency is readily obtainable. One or more siblings are usually affected. Occasionally the urinary difficulties can be traced back through several generations. Kanner<sup>8</sup> was able to elicit a history of enuresis in the immediate family of his patients (parents or siblings) in 47 per cent of his cases. In Stoekwell and Smith's<sup>14</sup> series a history of enuresis was obtainable in 63 per cent of the parents and in 21 per cent of the siblings. In Addis'<sup>14</sup> series 27 per cent of the parents and 20 per cent of the siblings gave a history of bed-wetting. If urgency and frequency had been included in their historical data an even higher percentage of familial involvement would undoubtedly have been obtained. Frary<sup>23</sup> concludes, from a study of fifty-nine clans in which there were one or more enuretic children, that enuresis is an hereditary trait determined by a single recessive gene substitution. In two families where both parents had been enuretic, all six children of these two matings were enuretic. We have observed one family where both parents were enuretic. Six out of the seven children in the family were enuretic.

A third characteristic is the persistence of the irritable bladder into adult life. Though the enuresis ordinarily disappears at or before puberty, urgency generally remains and in severe cases there may be nocturia or even a continuation of the wetting. Adults who have been persistent bed-wetters during childhood may function normally under usual circumstances but they develop urgency more readily than normal individuals when exposed to such stimuli as cold or nervous tension.

The act of voluntary micturition is an intricate process which depends for its proper functioning on the integrity of the nervous pathways which regulate conscious control, on proper innervation of the structures involved in the act, and on the correct anatomic arrangement of these structures.

*The Physiology of Micturition.*<sup>24</sup>—During the filling of the bladder intra-vesical pressure remains practically unchanged until a threshold is reached, at which level the pressure rises rapidly and active vesical contractions take place. Only then does the desire to micturate occur. At this critical pressure mild, rhythmic contractions of the detrusor muscle which opens the internal sphincter appear. The threshold may be lowered by a number of stimuli such as sounds, odors, temperature changes, coughing, laughing, straining, and by standing erect. With increase of bladder volume, a sensation of distention intrudes upon consciousness. The internal sphincter contracts and relaxes in reciprocal relationship with the detrusor muscle. It is entirely involuntary and its reaction to voluntary control is secondary to the behavior of the detrusor. It remains closed during intervals of slight or absent vesical contraction. The external sphincter, which is under voluntary control, also remains closed. It opens only after opening of the internal sphincter. When micturition is completed it closes before the internal sphincter. Voluntary control of micturition is effected solely by voluntary or subconscious inhibition of the mechanism of spontaneous reaction to distention.

The bladder is innervated by three sets of nerves.<sup>25</sup> The pudic nerve is voluntary and arises from the first three or four segments. It carries sensory fibers from the urethra and is the motor nerve to the external sphincter. The pelvic nerve, part of the parasympathetic nervous system, is also derived from the first three or four sacral segments of the spinal cord. It conveys most of the sensory impulses from the wall of the bladder and carries motor impulses to the detrusor, which opens the internal sphincter. The hypogastric nerve, part of the sympathetic system, transmits vesical sensation. Its motor functions are many: inhibition of the detrusor muscle; contraction of the ureteral meatus, trigone, internal sphincter, and smooth muscle of the prostate and seminal vesicles; transmission of vasomotor impulses to the bladder. Some investigators also have observed contraction of the detrusor muscle on hypogastric stimulation.

Cerebral control during the waking hours is unimpaired in persons with enuresis. The basic difficulty seems to be, rather, an excessive urge to micturition which requires immediate satisfaction. While awake the enuretic is fully aware of bladder distention but the need for emptying is so urgent that voluntary inhibition may be overcome and day-wetting takes place. During sleep the urgent need for micturition may awaken the person and he then empties the bladder; if he does not awaken, enuresis ensues. But whether he awakens or not the same mechanism is at work.

An explanation for the disturbance in bladder function, in some children at least, is found in the cystometric studies of McLellan<sup>26</sup> and others.<sup>27</sup> Bladder sensation—the feeling of distention—is normal or only slightly diminished. Bladder capacity is low normal. There is no residual urine. McLellan describes two types of abnormality in the response of the bladder to the introduction of



fluid, one or the other of which was found in all his patients with persistent enuresis. The first type was characterized by uninhibited rhythmic contractions of the detrusor occurring after the injection of every 25 to 75 c.c. of fluid, increasing in amplitude until the bladder capacity was reached, at which point the urgency from detrusor contraction necessitated prompt emptying of the bladder. The second type of abnormality was a smooth curve until bladder capacity was reached, at which point an uninhibited contraction of the bladder made emptying imperative. Similar changes were observed by Stockwell and Smith<sup>14</sup> in some of their children with enuresis. Nine of the twenty-five adults with enuresis studied by Forsythe and Karlan<sup>27</sup> also showed these changes. In thirteen others local uropathy was found and in only three was urologic examination negative.

The functional abnormality in some pollakiuric individuals then, appears to lie in the response of the bladder to distention. Bladder capacity is not strikingly diminished but, when capacity is reached, the call to micturition is sharp and the demand for relief immediate. In others the abnormality seems to reside in minor abnormalities in the region of the vesical outlet.

That psychic factors influence the condition, just as they influence urinary function in the normal individual, there can be no doubt. The agitation and concern of the child lest involuntary micturition occur serve to aggravate the difficulty. It is also self-evident that the habit of wetting the bed, with its social implications, will have its effect on the personality development of the child and this in turn may intensify the difficulty.

In summary, then, enuresis is looked upon as a hereditary abnormality in bladder function, the principal characteristic of which is an urgent need to empty the bladder. Cerebral control is normal but the call to micturition is so intense that voluntary inhibition may be overcome and wetting takes place. Presumably the basis is a structural abnormality in the bladder and proximal urethra or in the appropriate innervation. Children with this abnormality acquire bladder control with difficulty but they can be trained. If they live in an environment in which habits of cleanliness are poorly developed they are likely to wet the bed. But, even when carefully reared, they are much more prone to enuresis when subjected to emotional stress than are other children.

#### TREATMENT

The treatment of a patient with enuresis requires an understanding of the factors underlying the condition and a comprehension of the influence of the symptoms on the personality of the child. The therapeutic methods employed may represent a greater psychic trauma for the child than the condition itself, and this fact should always be kept in mind when a line of treatment is being formulated. Before undertaking treatment, a careful history should be taken in order to permit evaluation of the relative importance of irritable bladder, faulty training, and psychogenic factors. The urine should always be examined at the beginning of treatment. In patients who do not respond to therapy, the examination should be repeated several times, particularly for the presence of white blood cells. Factitious enuresis or voluntary wetting should be differentiated from true enuresis.

*Psychologic Management.*—The parents should be urged to assume an unemotional attitude toward the symptom. Great concern, severe censure, punishments, threats, deprivations and shaming aggravate the situation. Failure to live up to parental expectations, shame, fear of punishment, feelings of inadequacy, agitate the child unduly and make him anxious. Conversations with the child should be directed toward building up his self-confidence and ridding him of feelings of hopelessness, shame, and guilt. By relieving him of the burden of parental disapproval and, at the same time, giving him some understanding of the mechanism of his difficulty, nervous tension, which increases bladder irritability, is lessened.

The parents should be told that the child is not primarily at fault and that the abnormality has probably been inherited from one of them. The discussions in the doctor's office with the parents are best conducted in the child's presence. At home parental conversation with the child about the enuresis should be limited to encouragement and reassurance as improvement begins.

*Belladonna.*—Of the many drugs which have been used in the treatment of enuresis the only one which has survived is belladonna, first introduced for this purpose by Bretonneau. It is of benefit, if not curative, in the large majority of cases. Its favorable action is dependent on inhibition of the detrusor muscle which is innervated by the parasympathetic nervous system.

Amberg and Grob<sup>28</sup> studied the influence of atropine on the bladder function of children with enuresis. They found that in nine out of nineteen children a definite effect was produced. The pressure in the bladder was reduced even when the bladder contained larger amounts of fluid than before the administration of atropine, and the amplitude and the frequency of contractions were reduced. The bladder could hold more fluid without its escaping around the sides of the catheter, and, when discomfort was experienced, it was slight.

Belladonna, in order to be effective, must be given in large doses. One may safely start with 5 drops of tincture of belladonna (one drop is equivalent to  $\frac{1}{3},000$  grain or 0.02 mg. of atropine) 3 times a day for a 5-year-old child and increase the dosage by 3 drops each day (one drop each dose) until distinct improvement in the urinary symptoms or flushing of the skin appears. It is usually possible to give children with the irritable bladder large doses, up to 20 to 30 drops, three times a day. No improvement is to be expected until the dosage reaches between 10 and 15 drops. The first favorable effect is a lessening of the urgency and frequency during the day and then a decrease in the amount of urine voided during the night. Belladonna should be continued for eight to ten weeks after the enuresis has ceased in order to permit the habit of voluntary control to become established. Belladonna, by relieving the urgency and frequency, makes the patient more confident of his ability to control the urinary function. In this way the agitation and fear which intelligent children feel are relieved and a strong psychic factor in the mechanism is lessened. The child should sleep in a warm bed.

*Training.*—Treatment with belladonna should be combined with training and suggestion. Fluids should be limited in the late afternoon and a dry supper given. During the day an attempt should be made to prolong the intervals

between voiding for as long a time as possible. The child is awakened once or twice during the night, dressed in bathrobe and slippers, and walked to the toilet. Care should be taken that the child is fully awakened when he voids, since putting a sleeping child on the toilet has no value in bladder training. The number of times the child is awakened is diminished as he improves. Elevation of the foot of the bed may help.

*Rewards.*—The system of rewards is at times effective. The child is given a chart on which the days of the week are written and he is instructed to note the dry and wet nights. A gold star is given for each dry night. This method is most useful with children from 5 to 7 years of age who may be receiving stars for good behavior at school. It gives the child impressive evidence of improvement in terms which he can readily appreciate.

*Salt Therapy.*—Krasnogorski<sup>29</sup> has obtained good results in the treatment of enuresis by the administration of 5 Gm. of salt immediately before bedtime. The treatment is based on the fact that salt leads to a retention of water. The evening meal is given about two hours before bedtime and contains little salt but fluids as desired. The fluid given with the low salt meal is excreted by the time the child goes to bed. Immediately before the child goes to sleep he is given a sandwich made with salted herring, smoked salmon, bacon, or swiss cheese and salt butter. The amount of salt administered in this way is sufficient to reduce the urinary secretion during the night to 100 to 125 c.c. This method has also been used with success by Rosenson and Liswood.<sup>30</sup>

*Testosterone.*—Testosterone was first used for the treatment of disturbances of micturition in adults by Bodechtel.<sup>31</sup> He, and others subsequently, reported favorable results which were attributed mainly to improved tonus of the bladder muscle produced by testosterone. Zehn<sup>32</sup> used testosterone propionate in children with enuresis and reported uniformly good results.

Schlutz and Anderson<sup>33</sup> treated fifty enuretic children with male sex hormone preparations (thirty-six boys and fourteen girls). Methyltestosterone was given once daily, in refractory cases twice daily, in doses from 10 to 20 mg. In some cases testosterone was given by topical application to the abdomen twice daily, using about 8 mg. per day. When improvement occurred treatment was continued for two months. No other form of therapy except restricted fluids and a high salt intake was used. The children were awakened and made to urinate once during the night.

Of the thirty-six boys, twenty were entirely cured, eleven were improved, and five were unaffected. Of the fourteen girls, seven were completely cured, six were improved, and one showed no change. The boys seemed to respond more quickly than the girls. In thirteen of the twenty-seven cured cases, the results were prompt, occurring within two weeks.

*Benzedrine* is a useful aid in the treatment of enuresis when the child is markedly overactive or when there is reason to believe that much anxiety is present. The drug is given once a day on rising. The initial dose is 5 mg. a day. It is increased rapidly, up to 20 or 30 mg. if necessary, until a therapeutic or toxic effect is obtained.

*Conditioning.*—A number of apparatuses have been invented to condition children against bed-wetting. The Mowlers<sup>24</sup> have devised an apparatus which rings a bell when the child wets the specially constructed pad on which he sleeps. The child is then expected to go to the toilet. The device is used with the child's full knowledge and consent. The Mowlers report striking success with this method. Other conditioning devices release a stream of cold water or a blast of air when the child starts to wet.

In diurnal enuresis, when the ammoniacal smell is offensive, rinsing the underclothes in a saturated solution of boric acid or other antiseptic is helpful.

When general treatment is unsuccessful, the child should be referred to an urologist. Good results have been reported following urethral dilatation.

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# Comments on Current Literature

## ACTIVE IMMUNIZATION AGAINST TUBERCULOSIS

IN THE September issue of the *American Review of Tuberculosis*, Joseph D. Aronson<sup>1</sup> reports results of an 11-year study concerned with evaluation of the efficacy of BCG vaccine in active immunization against tuberculosis. Reviewing the literature, the author attempts to appraise various vaccines that have been prepared for this purpose. Neither tuberculin nor the metabolic products of tubercle bacilli has been shown to have real value for increasing resistance to infection. Tubercle bacilli modified or killed by the action of chemicals may give slight or transitory immunity to animals, but most results are equivocal. Exposure of tubercle bacilli to radium emanations, to ultraviolet light, and to heat, has given only suggestive results. The use of heterologous types of mammalian tubercle bacilli has given varying results. Of considerable interest was the use of vaccine prepared from a murine type of acid-fast organism isolated from the vole. This vaccine seems to have had definite value for increasing resistance to infection. There have been many studies, both in animals and man, which indicate that viable tubercle bacilli produce best and lasting immunity; nevertheless, it is the consensus that the use of an unattenuated viable and virulent organism in man is unsafe.

It working with cattle, Calmette and Guérin found that resistance to reinfection was due to the presence of viable tubercle bacilli, and that by injecting animals with a vaccine prepared from an attenuated strain of tubercle bacilli, protection against re-infection was demonstrated. The results of this animal experimentation suggested the use of this vaccine, called BCG, for the active immunization of man. Initially, in 1921, Wilde Hall administered BCG per os to a newborn infant. The oral route of administration was recommended at this time since the intestinal mucosa of the newborn infant was thought to be permeable to the passage of bacteria. Because of inconstant results with this method of administration the subcutaneous route was tried, but a significant number of patients developed cold abscesses which had to be aspirated or treated surgically. Wallgren then suggested the intracutaneous injection of the vaccine. This method is now the procedure of choice. Associated development of a localized, slowly healing ulcer at the site of inoculation and the rare occurrence of ulceration of regional lymph nodes are cited as objections to the procedure, but neither is regarded as serious.

Aronson availed himself of an excellent opportunity to study the effectiveness of BCG vaccine toward the control of human tuberculosis in a population having a high morbidity and mortality. The project was carried out in cooperation with the Health Division of the Office of Indian Affairs, Department of the Interior. The work was begun in 1935, using Indian Agencies, distributed through Arizona, Wyoming, North Dakota, South Dakota and Alaska.

A survey of the incidence of tuberculosis in these various areas was made. Since a positive reaction to tuberculin is generally interpreted as being associated with increased resistance to reinfection, this criterion was used in deciding which patients should receive active immunization with BCG vaccine. The use of BCG or other immunizing agents is not indicated in those subjects who react to tuberculin. Conversely, specific immunization with BCG does seem indicated in those individuals who have escaped natural infection and who, therefore, fail to react to tuberculin.

Pertaining to the control of the clinical study, Aronson points out that the significance of any controlled study depends to a large extent on the quality of the samples. The group studied must be comparable and the selection of members of the groups must be made without bias. To meet these requirements a record was prepared for each person who failed to react to tuberculin. An alternate division of the records was made. Approximately one-half received BCG vaccine, while the remaining number served as controls.

The technique of vaccination was as follows: the BCG culture was maintained on potato media and was transferred to bile potato at regular intervals. There were thirteen different lots of vaccine prepared in the portable laboratories in each agency. No other culture was kept in the laboratory and, to minimize the danger of contamination with tuberculous material, the laboratory was set up in a vacant room at a distance from the hospital. Each patient received intracutaneously 0.1 c.c. of the vaccine containing 0.1 or 0.15 mg. of the moist bacillary mass. Injections were made as superficially as possible on the skin over the deltoid muscle. Within forty-eight hours of the intracutaneous injection, there appeared a sharply defined, reddened nodule about 4 mm. in diameter and 1 mm. in height. Approximately three to four weeks after vaccination the nodule rapidly increased in size and in many instances a definite central area of softening was noted. Ulceration occurred by the fourth week in 75 per cent of the cases. The ulcers healed, leaving small scars. In no instance did lymph nodes ulcerate, although in about 5 per cent there was some evidence of increased size of regional lymph nodes.

Of the 3,008 persons included in this program, approximately 85 per cent were examined roentgenologically at the same time that the initial tuberculin test was carried out. A positive tuberculin reaction following the administration of BCG was interpreted as evidence of the establishment of an initial or primary tuberculous focus.

It is of considerable interest that one year after vaccination, 93.3 per cent of those tested with tuberculin had positive tests. In the unvaccinated control group only 12.7 per cent reacted positively to tuberculin.

The use of roentgenograms, although not entirely an objective procedure, seemed to offer the best medium for determining the presence and nature of pulmonary lesions. It was found that, with the exception of pleural effusion and pleural thickening, lesions showing the roentgenologic characteristics of tuberculosis were significantly more frequent among the controls than among the vaccinated.

The most striking evidence of the efficacy of BCG vaccine is brought out when total mortality rates and mortality rates from tuberculosis are compared in the vaccinated and control groups. Of the 1,551 vaccinated, a total of fifty-five persons died from all causes during the nine- to eleven-year period of this study. During the same time 109 of the 1,457 controls died from all causes. In the BCG vaccinated group there were 3.1 deaths per 1,000 person years, whereas in the control group there were 7.2 deaths per 1,000 person years of observation. In the BCG group six died from tuberculosis during the course of the study, while among the controls fifty-three died from this disease. The mortality rate from tuberculosis per 1,000 person years of observation is 0.4 for the vaccinated and 3.5 for the controls.

An interesting portion of the paper deals with the effectiveness of BCG vaccine among newborn infants. This study was carried out in a group of newborn infants for approximately five years. From December, 1938, to December, 1940, 123 newborn infants were vaccinated intracutaneously with 0.1 mg. of BCG vaccine within several days after birth. During the same period of time 139 newborn babies were untreated and served as controls. At

the time of their first tuberculin test, these children ranged in age from 3 to 14 months. At this time, 85 per cent of the vaccinated and 77 per cent of the control group were tuberculin tested. An analysis of the testing indicated that 91 per cent of the vaccinated and 3.7 per cent of the controls reacted positively to tuberculin. In 1946 this same "newborn" group ranged in age from 6 to 8 years. Of this group, 82 per cent were retested with tuberculin. Among the vaccinated the tuberculin test was positive in 80 per cent, whereas among the controls, positive reaction to tuberculin was noted in 26.5 per cent. During the six to eight years of observation, primary tuberculosis on x-ray examination was noted in four of the 123 vaccinated children and in eleven of the 139 controls. Of the seven deaths among the vaccinated cases, none had been from tuberculosis, while of the fifteen deaths among the controls, four were due to tuberculosis. These four deaths all occurred within the first three years of life.

Contrary to the common objection that the use of BCG threatens possible danger of increasing virulence in the live bacillus, Aronson contends that the attenuated viable BCG strain of tubercle bacilli is an effective and safe immunizing agent. He points out that innocuousness of the BCG vaccine for man is proved by the fact that millions of persons all over the world have received the vaccine and not a single unequivocal case of tuberculosis attributed to its use has been reported. While the author is aware that clinical studies in human beings over a long period of time are difficult to interpret, he believes there is considerable circumstantial evidence indicating that the use of the vaccine has reduced the morbidity and mortality from tuberculosis. The recent objection to the widespread use of BCG vaccine based on the premise that tuberculin reaction following use of BCG would mask the tuberculin reaction, thus making it more difficult to detect sources of tuberculous infection, seems valid. The advisability of universal use of BCG vaccine is subject to difference of opinion. Aronson believes that the use of the vaccine is definitely indicated where tuberculin-negative persons are likely to be exposed frequently to tuberculous infection.

The work of Aronson and his group is an outstanding contribution to our knowledge concerning active immunization against tuberculosis of human subjects. Only by such long-term and controlled studies involving large numbers of the population can a clearer understanding of this controversial and highly important subject be gained.

RUSSELL J. BLATTNER

#### REFERENCE

1. Aronson, J. D.: *Protective Vaccination Against Tuberculosis With Special Reference to BCG Vaccination*, *Am. Rev. Tuberc.* 58: 255, 1948.



## News and Notes

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Dr. Hugh McCulloch has retired from practice in St. Louis and has moved to Chicago where he will be Medical Director of the Rheumatic Fever Program for the Chicago Heart Association and Medical Director of the LaRabida Sanitarium for Research in Rheumatic Fever.

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Dr. James B. Arey, formerly with the Department of Pathology at Tulane University, is now Pathologist at St. Christopher's Hospital for Children, Philadelphia, and is also responsible for the pediatric pathology at Temple University Hospital.

At St. Christopher's Hospital a Tumor Diagnostic Service will be developed which will be available to other hospitals in the State and adjacent territory.

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Dr. Joseph Stokes, Jr., delivered the seventeenth annual series of the Benjamin Knox Rachford Lectureships on Feb. 1 and 2, 1949, at the Children's Hospital Clinic and Research Building, Cincinnati, Ohio. The general title of his lectures was "Viral Hepatitis."

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The annual meeting of the Society for Pediatric Research will be held at Atlantic City May 3 and 4, 1949.

The annual meeting of the American Pediatric Society will be held at Atlantic City May 5 and 6, 1949.

Both societies will meet at the Marlborough-Blenheim Hotel.

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The American Board of Pediatrics has announced that the dates for the Examinations in Baltimore have been changed to May 7, 8, and 9, 1949.

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The following were certified by the American Board of Pediatrics at the Examination in Atlantic City, N. J., Nov. 17, 18, and 19, 1948.

Dr. Adams, Frederick Merrill	322 Wabeek Building, Birmingham, Mich.
Dr. Allen, Reginald Anthony	223 Thayer St., Providence, R. I.
Dr. Alsever, William Dewey	836 Lancaster Ave., Syracuse 10, N. Y.
Dr. Altenau, Grace A.	725 4th Avenue, Brooklyn 32, N. Y.
Dr. Amick, Perry P.	310 Bankers Trust Building, Des Moines, Iowa
Dr. Batson, Oscar Randolph	Vanderbilt University Hospital, Nashville 4, Tenn.
Dr. Bleiberg, Nina	4153 49th Street, Long Island City 4, N. Y.
Dr. Burton, Irving Frederick	14608 Gratiot Ave., Detroit, Mich.
Dr. Cagan, Maclyn	60 Ridge Road, North Arlington, N. J.
Dr. Casey, Vincent P.	3105 Roberts Ave., New York City, N. Y.
Dr. Cohn, Walter L.	511 Cottman Street, Philadelphia 11, Pa.
Dr. Crump, Edward Perry	Meharry Medical College, Nashville, Tenn.
Dr. Dickson, William Anderson	266 Beacon Street, Boston, Mass.
Dr. Diekstein, Benjamin	6725 Castor Avenue, Philadelphia 24, Pa.
Dr. Dyer, Edward C.	330 Dartmouth Street, Boston 16, Mass.

Dr. Erganian, Jane A.  
 Dr. Evans, Katharine W.  
 Dr. Fischman, Mervin Edward  
 Dr. Friedman, William C.

Dr. Geib, Margaret Eugenia  
 Dr. Gregory, Elizabeth Alice  
 Dr. Harris, Howard Yeager  
 Dr. Harris, Ruth Cameron

Dr. Hunt, Andrew Dickson, Jr.

Dr. Hyman, Mary Elizabeth  
 Dr. Kerley, J. Hoyt  
 Dr. Kety, Josephine Gross

Dr. Klein, Harold  
 Dr. Knox, Joseph C.  
 Dr. Krafchik, Louis L.  
 Dr. Krugman, Saul

Dr. Leonard, Martha Francis  
 Dr. Leslie, Warren D.  
 Dr. Lublin, Ann  
 Dr. Lyle, Donald Fraser  
 Dr. Marks, Lillian  
 Dr. McDougall, Clarice L.  
 Dr. MeKey, John D.  
 Dr. Putnam, Henry Mitchell  
 Dr. Robinson, Arthur  
 Dr. Root, James Harold, Jr.  
 Dr. Rosenberg, Jonas Samuel  
 Dr. Ross, Maurice  
 Dr. Siker, Estelle  
 Dr. Sims, Arthur I.  
 Dr. Steigman, Alex J.

Dr. Viek, Edward Hoge  
 Dr. Whitehead, Betty Willis  
 Dr. Willner, Milton Michael  
 Dr. Yarow, Natalie  
 Dr. Zarehy, Alex C.

122 Rodney Street, Glen Rock, N. J.  
 8236 Germantown Avenue, Philadelphia 18, Pa.  
 264 Clinton Place, Newark, N. J.  
 Glenwood Terrace Apts., 1409 Greenport Road, Far  
 Rockaway, N. Y.  
 1277 Clinton Place, Elizabeth, N. J.  
 255 Massachusetts Ave., Arlington, Mass.  
 40 James St., Kingston, Pa.  
 Babies Hospital, 3975 Broadway, New York City,  
 N. Y.

Children's Hospital, 1740 Bainbridge Street, Phila-  
 delphia, Pa.

45 East 82nd Street, New York 25, N. Y.  
 167 East 82nd Street, New York City 28, N. Y.  
 Children's Hospital, 1740 Bainbridge Street, Phila-  
 delphia 46, Pa.

522 Eastern Parkway, Brooklyn, N. Y.  
 15 North 5th Street, Wilmington, N. C.  
 158 Livingston Avenue, New Brunswick, N. J.  
 Children's Medical Service, Bellevue Hospital, New  
 York City 16, N. Y.

55 North 5th Avenue, Highland Park, N. J.  
 Riley Law Building, Room 400, Wheeling, W. Va.  
 18472 Whitcomb Street, Detroit 19, Mich.

5711 Thomas Avenue, Philadelphia 43, Pa.  
 1270 Bryden Road, Columbus, Ohio  
 616 Medical Arts Building, Grand Rapids, Mich.  
 320 North Main, Orlando, Fla.

743 High Street, Dedham, Mass.  
 908 Magnolia Street, Denver 7, Colo.  
 103 North Main St., Waterbury, Conn.  
 219 Washington Avenue, Batavia, N. Y.  
 372 Main Street, Saco, Maine  
 301 Westchester Avenue, Port Chester, N. Y.  
 3215 Columbia Pike, Arlington, Va.

Children's Hospital, Elland Ave. & Bethesda, Cin-  
 cinnati 29, Ohio

323 North Narberth Avenue, Narberth, Pa.  
 Chatham, Va.

822 South 12th Street, Newark, N. J.  
 1215 Fifth Avenue, New York City, N. Y.  
 593 Central Avenue, Cedarhurst, N. Y.

## Book Reviews

**Nursing for the Future.** Esther L. Brown, Ph.D., New York, 1948, Russell Sage Foundation, 198 pages. Price \$2.00.

This study and report, prepared for the National Nursing Council by the Director of the Department of Studies in the Professions of the Russell Sage Foundation, is by far the most intelligent and thought-producing discussion of nursing and nursing education that has appeared. It should be carefully read by all who are involved in the chaotic situation which exists today in nursing. To summarize briefly, the theme of the report is that the large majority of hospital nursing schools, as they have existed for the training of the R.N. over the past years, will and must go out of existence. Nursing in the hospitals and "private duty" nursing will be largely taken over by "nurse assistants" who are in reality trained "practical nurses." On the other hand, the "professional nurse" will evolve a product of the university schools of nursing which grant degrees. This will attract a better type of men and women nurses who will look upon and make nursing a real profession. From this group will come the nursing educators, administrators, and specialists. The transition from the present situation will come gradually and many things will be required. Among these are the legal status and definition of the nurse assistant and her training as nearly all our nursing laws relate to the R.N. Most important is the strengthening of the university schools for the education of the "professional nurse," as today some are in a precarious situation, and all are greatly in need of income comparable to the other professional schools conducted by the universities and which is necessary to place them on a basis of equality. The report aptly compares the educational situation as it exists today in nursing with the medical school situation as it existed before the Flexner report and the work of the A.M.A. some forty years ago. Much of the impetus to reorganize nursing education and to change the pattern of nursing care which grew up around the hospital school training of the R.N. comes from the nursing leaders, which augurs well. Sane, broad-visioned, objective discussions such as this will go a long way in shaping the future of nursing.

B. S. V.

**Medical Research in France During the War (1939-1945).** Paris, 1948, Éditions Médicales Flammarion. (A collection of thirty articles gathered and presented by Prof. Jean Hamburger with a foreword by Prof. Pasteur Vallery-Radot.

Prof. Hamburger has gathered and presented in English in this book of 306 pages a group of thirty interesting articles reporting medical research in France during the war years. It covers all fields of medical science. A few are of interest to the pediatrician. Prof. R. Debré and his associates describe a new disease, or a neuro-oedematous syndrome, that they observed in children, in which in addition to pain and a peripheral type of paralysis is characterized by a diffuse generalized edema. The spinal fluid is normal and there are no urinary changes. They consider it of epidemic nature caused by a neurotropic virus. Prof. G. Ramon, to whom the world owes so much for his work on anatoxins (toxoids), makes a plea for the more extensive use of diphtheria toxoid throughout the world. He quotes British figures to show not only its effect in reducing diphtheria morbidity, but the low mortality of diphtheria when it develops in immunized individuals. An interesting article on hunger osteosis occurring during and as a result of the war is presented by Dr. Justin-Besançon. To the reviewer, the collection leaves two impressions: first, the courage with which the French physicians carried on and held to their ideals of medical science during the war when their life was one of misery; second, from the paucity and incompleteness of the studies presented the tragic effect of the war and German occupation on French medicine—and medical research. The book was made possible through the generosity of the Rockefeller Foundation. To the reviewer, it is a book of real interest and a worthy tribute to our French colleagues.

B. S. V.

**Technique of Treatment for the Cerebral Palsy Child.** Paula F. Egel, St. Louis, 1948, The C. V. Mosby Company, 203 pages.

Miss Egel has had great experience in working with children with cerebral palsy. She has been thoroughly indoctrinated at Baltimore by Dr. Winthrop Phelps and feels sure that the stage is set for a manual based on entirely lucid explanations of the physiological disturbances seen in the chaotic groups which form the enormously complex "entity" of cerebral palsy.

It is fair to quote directly a few statements which indicate the method of presentation.

"Damage to certain areas of the brain, no matter how caused, produces a specific type of involvement in one or more muscles. The site of involvement depends on the site of the brain damage, since each muscle in the body is controlled by a definite area of the brain."

"Cerebral palsy cases have been divided into five main general types, namely: spastic, athetoid, tremor, ataxic and rigidity. The spastic is a pyramidal tract condition and cortical in origin. The damage which produces spasticity lies directly behind the frontal or thinking area, and it is the only type which may or may not have mental impairment due to the identical injury."

"Feeble-mindedness, if found in the athetoid, has no relation to the athetoid condition since the basal ganglia, unlike the motor cortex, is far from the frontal lobe."

It seems impossible to believe that discussion which is based on such brief and entirely unconventional statements will be helpful to the newcomer and certainly many experienced people will read no further.

However, abandoning a manual on physical therapy because one is confused by the introduction is illogical. As a matter of fact, the chapters on physical therapy are useful and the diagrams and pictures are clear. Furthermore, there is every reason to agree that the clinic in Buffalo is well conducted and that this manual will be of the greatest help to workers who are starting new clinics.

This reviewer left this very interesting book with the feeling that the inadequate discussion at the start might well have been omitted or even better should have been rewritten.

B. C.

**Technic of Medication.** Austin Smith, M.D., Director of the Division of Therapy and Research; Secretary, The Council on Pharmacy and Chemistry, The American Medical Association. Philadelphia, 1948, J. B. Lippincott Co. 248 pages. Price \$4.00.

This book is intended to serve as a guide for the physician in the methods of applying drugs and other treatments by the available routes—oral, parenteral, local, rectal. Discussions of prescription writing and the care of essential equipment are also included. A rather extended presentation of the methods of "supportive" therapy in vogue some years ago is given: the techniques of manufacture and application of stupes, mustard plasters, poultices, and other "counter-irritative" devices are accorded more than ample space.

A re-edition of the late Bernard Fantus' *General Technic of Medication* (1938), this work has surprisingly little to say about many of the techniques developed during the intervening ten years. For example, such important considerations as oxygen therapy, the proper composition of parenteral fluids, caudal anesthesia, the use of hot packs in poliomyelitis and of the "cold" humidifier in respiratory diseases receive but scant attention. A bare one-half page is devoted to the subject of blood and plasma transfusion; the omission of any mention of such matters as the Rh factor and serum hepatitis is regrettable. No attempt has been made to develop the subject of scalp vein infusion or of the "cut-down" technique for continuous venoclysis in infants.

The book cannot be recommended for pediatricians.

G. F.

## Editor's Column

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SIR LEONARD PARSONS, KT., F.R.S.

THE recent election of Sir Leonard Parsons to the Fellowship of the Royal Society is a well-merited honor which has brought pleasure to his many pediatric friends and colleagues throughout the world.

The *Birmingham Medical Review* has issued a "Complimentary Number" in his honor, which contains a biographical sketch and the speeches made at a dinner given him in recognition of the honor by the medical faculty of the University of Birmingham, of which he is Dean and Professor Emeritus of Paediatrics and Child Health. In addition, three of his addresses have been reprinted. One of these, "Research in Paediatrics (a Backward and Forward Glance)," was delivered at the dedication of the Children's Hospital Research Foundation in Cincinnati in 1931. Another on "Paediatrics—Its Contribution to Medicine" quotes the famous poem by John Rurah on pediatric psychiatry which was published in the JOURNAL in 1932. The third on "The Clinician and the Rh Factor," delivered at Glasgow in 1947, represents the field of the anemias in which Sir Leonard Parsons has made so many distinguished contributions.

The Royal Society was founded in 1662 and election to the Fellowship is as high an honor as can be achieved by a British scientist. On behalf of his many friends on this side of the Atlantic, the JOURNAL extends its congratulations for the deserved honor to a distinguished pediatric colleague. We are proud that his name is on the rosters of the American and Canadian Pediatric Societies as an Honorary Member, and of the American Academy of Pediatrics as Honorary Fellow.

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### THE HOOVER REPORT

A RATIER unusual Christmas packet was the release on December 25 of that part of the report of the Hoover Commission on Organization of the Executive Branch of the Government which deals with medical affairs. There is enough political and administrative dynamite in it to have made its release more appropriate for July 4. Nearly every newspaper headlined the waste in the present Federal expenditures for hospital construction which the report brought out, but only a few discussed the proposed administrative changes which are of more significance to the medical profession. We hazard the guess that the timing of the release is in some way connected with the President's report on the State of the Union to be presented on the opening of Congress on January 5, which will not be available until after the forms for this issue of the JOURNAL are closed. Whether it is simply a pacemaker for a proposal for a new Cabinet department, or whether it is intended to

counteract the socialistic trend of medical participation on the part of the Federal government remains to be seen, and it will doubtless be the subject of much argument.

The "task force" of sixteen who prepared the report—of whom eleven are "medical authorities"—ruled that the controversial subject of compulsory health insurance was outside the scope of the inquiry. The report is predicated on the assumption that there will be a new Cabinet department to include health, education, and welfare, which will take over the functions of the present Federal Security Agency as well as a number of other bureaus and agencies. The possibility of a Cabinet department for health alone was "excluded from consideration."

In this new department a national bureau of health is to be set up with a physician at the head who reports only to and directly to the Cabinet officer, but the report specifically states that any administrative undersecretary should not be a physician. The bureau itself, the report recommends, should be set up in three divisions.

1. *Medical Care.* This to include all Federal hospitalization, as the general hospitals of the military establishments, and all medical establishments of the Veterans Administration.

2. *Public Health.* The present functions of the Public Health Service of making grants-in-aid for medical research and training, with the exception of grants-in-aid in that particular field, would be taken away. The present Food and Drug Administration would be added.

3. *Research and Training.* The research programs of the National Institute of Health at Bethesda for cancer, mental health, etc. (now under the P. H. S.), would be included in the division, as well as such matters as medical and nursing education and training.

The wayward child in the medical picture as it now exists, the Children's Bureau would remain as a unit to work for the "whole child," but its program for maternal aid and crippled children would be transferred in three years to the new health bureau.

We fully agree with the report that fundamental to any health service Congress must first decide such questions as who is entitled to receive what benefits? Among the questions are ones as to whether or not medical services should be extended to all veterans irrespective of financial need, the matter of veterans with nonservice-connected disabilities, and the medical care of the families of service men. Interestingly enough, the report, while side-stepping the subject of compulsory health insurance, suggests a plan of voluntary insurance for veterans, with the government paying the premium where the veteran could not. The report thus automatically, whether intentionally or not, enters into the field of social and political controversy.

Considerable discussion is given to the uneconomical present policy of building Federal hospitals all over the country by the military and veterans' services, in competition with each other and with community hospitals being erected under the grants-in-aid program of the Hill-Burton Act. The high

cost of Federal government-built hospitals is stressed. It is estimated, for example, that the \$100,000,000 spending program for Federal hospitals in the New York area is unnecessary, and that for the country at large it is well over one-half billion. On the other hand, in contrast to the hospital construction program, the report praises the personnel system of the Veterans Administration under which private specialists are employed on a part-time basis, and recommends the extension of this method as far as possible in all government hospitals.

In general, the report may be considered as recommending that Federal subsidies and Federal aid be channeled to the upbuilding of medical schools and medical research, and to community and private hospitals, with a minimum of supervision by the Federal government, rather than the extension of government-constructed and maintained hospitals.

The political and social implications of the report are obvious and it is easy to see the furor that will be raised by certain of the veteran organizations and by bureaus already entrenched. With a rising cost of government and a Federal deficit in the horizon in 1949 and 1950 in contrast to the surplus in 1947 and 1948, perhaps Congress will listen to the Hoover report rather than the special interests involved. Anyone who has watched the mushrooming of Federal medical developments and participation in recent years fully realizes the need for administrative reorganization and a clear-cut, definite policy on the part of the Federal government.

B. S. V.

# The Journal of Pediatrics

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## Original Communications

### A COMPARISON OF PARADIONE AND TRIDIONE IN THE TREATMENT OF EPILEPSY

JEAN P. DAVIS, M.D., AND WILLIAM G. LENNON, M.D.  
BOSTON, MASS.

THE value of trimethyloxazolidine dione (Tridione) in the treatment of petit mal epilepsy has been abundantly demonstrated<sup>1, 2, 3</sup> However, reports of side effects, notably the induction of aplastic anemia in a handful of cases,<sup>4</sup> have sharpened the search for an analogue that might be equally helpful clinically but have less toxic action. The manufacturers of Tridione have developed the analogue dimethylethyl oxazolidine dione which they have named Paradione. The drug has been given the required tests for toxicity in the pharmacology department of Abbott and Company, but it is not yet on the market. Dr. R. K. Richards kindly supplied us with material.

The structural formula of Paradione differs from that of Tridione in the substitution of an ethyl for a methyl group on carbon 5. It is an oily liquid, slightly soluble in water but easily soluble in alcohol. It is supplied as an elixir (32 per cent alcohol) in which a fluid ounce contains 3 Gm., or a teaspoonful (4 c.c.) contains 375 mg. It is also put up in gelatin capsules, each containing 300 mg. Patients treated by us, if under 6 years of age, were given 8 c.c. or 750 mg. daily, and if above that age, from 12 to 24 c.c. daily. The dosage of Tridione was similar.

We have used Paradione during the past two years in a total of eighty-five patients. Its action in forty-seven patients has been published.<sup>5</sup> The present report deals with seventy-three patients subject to petit mal who took Tridione and Paradione successively, thirty-one patients subject to grand mal and nine subject to psychomotor seizures. Some experienced more than one type of seizure. The great majority of the patients were children. We were concerned first with the therapeutic effect of Paradione in various types of seizures, and second with the presence or absence of side effects.

#### PETIT MAL TRIAD

Most interest attaches to the patients who took both Tridione and Paradione. The periods of medication were comparable for the two drugs. Tridione was

From the Neurologic Institute of the Children's Medical Center, Boston.  
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used first. Paradione was substituted because Tridione failed to control seizures (70 per cent), or it caused unpleasant side effects (25 per cent) or the substitution was experimental (5 per cent).

There was no uniformity in the anti-petit mal action of these two drugs, patient A would prefer Tridione and patient B Paradione. In order to avoid a complicated presentation of data, we compare the therapeutic effects of the two drugs in the whole group of patients rather than in individuals. The reader should understand that this is a selected group of patients, selected in large part because of failure to respond satisfactorily to Tridione. Therefore, results do not represent the value of these drugs in the treatment of petit mal. Thus, in an unselected group of patients, 63 per cent were substantially improved by Tridione<sup>1</sup> against only 23 per cent in the present group.

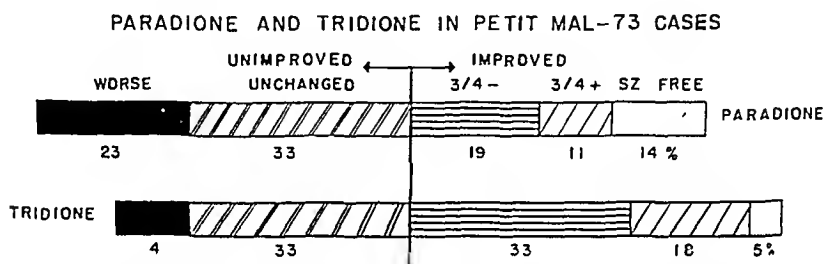


Fig. 1—Comparison of therapeutic results from Tridione and Paradione in the same seventy-three patients subject to petit mal. The portion of the columns to the right of the perpendicular represents various degrees of improvement, namely 100 per cent, 75 per cent or more, and less than 75 per cent. To the left are patients not improved, or (solid portion) those made worse.

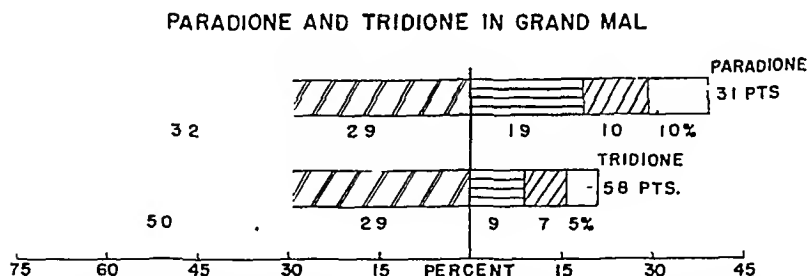


Fig. 2—Comparison of therapeutic effect on grand mal in thirty-one patients taking Paradione, and another fifty-eight patients taking Tridione. The symbols are the same as in Fig. 1.

Results in these seventy-three patients are displayed graphically in Fig. 1. The number of patients who lost three-fourths or more of their seizures was approximately the same whether Tridione or Paradione was used. (23 and 25 per cent respectively). When taking Paradione, more patients were seizure free, but also more were worse than when taking Tridione. For the whole group, this tabulation suggests that the action of the two drugs does not differ significantly. However, we have the general impression that Tridione is usually the more effective of the two. Only 5 per cent of the total group responded well to both drugs, the rest were greatly helped by only one of the two homologues.

The physician deals not with a group average, but with a succession of individuals. For each of these the effect of medication is unpredictable. A number of the patients treated had fewer seizures with Paradione than with Tridione. This consideration should make Paradione a useful substitute in therapy.

#### GRAND MAL

Thirty-one patients having grand mal, usually in addition to petit mal, were treated with Paradione, often combined with an anticonvulsant. Results in this group, compared with results with Tridione in a group of fifty-eight patients previously reported<sup>1</sup> is shown in Fig. 2. Because these two groups of patients are not identical, comparison is not exact. However, the data suggest that Paradione is not as much of a convulsant for patients as Tridione and, therefore, would be preferable for use in persons whose petit mal condition is complicated by grand mal.

#### PSYCHOMOTOR

Although DeJong<sup>6</sup> recommended Tridione (in addition to an anticonvulsant) for patients subject to psychomotor seizures, other investigators have not confirmed his optimistic reports. Our own results have been equivocal. In thirty-five cases previously reported,<sup>1</sup> 45 per cent were somewhat better. With Paradione, three out of nine psychomotor patients in the present series were improved.

#### SIDE EFFECTS

Many a promising anticonvulsant has had to be abandoned because of unpleasant or dangerous side effects. Those side-effects attending the use of Tridione have been peculiar or disconcerting. The principal ones are neutropenia, rash, photophobia, and sedation, the last named expressed as drowsiness, lethargy, or fatigue.

Comparison of the incidence of these symptoms in the 73 patients taking both of the diones is shown in Table I.

TABLE I. SIDE EFFECTS IN SEVENTY-THREE PATIENTS

	PARADIONE		TRIDIONE	
	NO.	%	NO.	%
Neutropenia				
1,600 to 2,200 per cubic millimeter	5	8	6	8
Below 1,600	4	6	9	13
Rash	11	15	15	21
Photophobia	9	13	24	33
Lethargy	8	11	3	4

We emphasize that the incidence of toxic reactions is high in this group of patients because of its selection. One-fourth were changed from Tridione to Paradione in the effort to avoid the side effects of Tridione. Of these various side effects, depression of the bone marrow, although relatively infrequent, is most serious. Thus, among 123 unselected patients treated for petit mal with Tridione only 6 per cent developed neutropenia of 1,600 cubic millimeters or

less.<sup>4</sup> Experience of others has varied greatly; for example, neutropenia was not observed in thirty patients treated with Tridione in the New Haven Clinic.<sup>7</sup> Severe neutropenia (a neutrophile count of 1,600 per cubic millimeter or less) occurred in 13 per cent of the present group of patients taking Tridione compared with 6 per cent taking Paradione.

Among these seventy-three patients, ten had an unfavorable blood reaction to Tridione but not to paradione; six reacted to both drugs, the reaction to both being severe in one case, more severe to Tridione in four, and more severe to Paradione in one case; three reacted to Paradione but not to Tridione. Thus, on all counts the Paradione would seem to have somewhat less toxic action on the bone marrow. This differential has permitted some patients to remain free of petit mal who otherwise would have had to cease medication with consequent return of seizures. The rule of stopping medication when this degree of neutropenia (1,600 per cubic millimeter) is reached, is of course, arbitrary. Possibly no harm would result from a neutrophile count that is persistently below 1,600 per cubic millimeter. We did not attempt to find out.

The case of L. B., first recorded in December, 1945,<sup>1</sup> illustrates the difficulty often encountered in maintaining medication and shows the comparative action of Tridione and of Paradione over periods of nineteen and twenty-two months, respectively. This child was born in February, 1942. A few days later ptosis of the left eyelid was noted. At 15 months of age she began to have a few clonic jerks of her extremities whenever she tripped or was startled by a noise. At 36 months she began to fall and jerk without tripping and to blink her eyes briefly (akinetie and pyknoleptic manifestations of petit mal). The akinetie attacks rapidly became more frequent. She would fall from fifty to 200 times a day. Phenobarbital gave a respite of only six days. The child was mentally retarded and her behavior was atrocious.

In March, 1945, Tridione, 0.9 Gm. a day, was prescribed. After twelve hours all seizures ceased. During the three and three-fourths years that have intervened the child has been almost free of seizures except when medication was interrupted. However, the dosage has had to be adjusted frequently. An incomplete fall or an episode of blinking could be observed several times a month and persisted even with a dose of 1.5 Gm. of Tridione daily. However, after the first six months the child made steady progress in mental development and in deportment. The necessity of periodic blood examinations was not realized until sixteen months after starting Tridione. Neutrophiles then numbered 3,400 per cubic millimeter, but two months later the count was only 1,700 and Tridione was stopped. Four days later neutrophiles had increased to 2,900 per cubic millimeter. The child began again to fall and on Oct. 4, 1948, Paradione was substituted.

The father of L. B. is a physician and forty-four blood examinations were made during the twenty-five months of Paradione medication. On four occasions the neutrophile count fell below 1,600. On the first three occasions, Paradione was stopped and akinetie attacks promptly recurred. Phenobarbital relieved for six days and bromides not at all. Four months later the neutrophiles numbered only 1,100 per cubic millimeter, but in four medicineless days

rose to their usual level of 2,500 per cubic millimeter. For the next twelve months the dose of Paradione was from 0.6 to 0.9 Gm. daily, together with 10 to 15 mg. of folic acid. Neutrophils numbered from 2,000 to 3,100 per cubic millimeter, eosinophils from 3 to 17 per cent and an incomplete fall or blinking was observed only at intervals of weeks. Although much improved, the electroencephalogram still contains spike and wave discharges. On June 15, 1948, a neutrophil count of 960 was obtained. Paradione was stopped for two days and then resumed at 0.3 Gm. daily. Four examinations made during the following six weeks revealed neutrophil counts ranging from 1,140 to 2,200 per cubic millimeter. On July 31, 1948, phenacetylurea (Phenurone) was added. After a rash, an infection, and another dip to 1000 neutrophils, affairs stabilized and the child has been symptom-free with normal blood for three months, taking only 0.3 Gm. Paradione and 0.5 Gm. Phenurone daily.

As regards the complication of cutaneous rash, experience with the two drugs was much the same; i.e., 15 per cent experienced a generalized rash with Paradione against 21 per cent with Tridione. Of eleven patients who displayed an eruption while taking Paradione, in five the rash was morbilliform, in three urticarial, and in one each eczematoid, hemorrhagic, and acneiform. Of the fifteen patients taking Tridione, twelve had a morbilliform, two an acneiform, and one an eczematoid type of reaction. Paradione might have been favored by the circumstance that Tridione was given first. This may have had the effect of desensitizing patients. Some persons who have a rash when medication is first instituted will not erupt when, after an interval, the drug is reinstated.

Hemeralopia (photophobia) is a curious side effect of Tridione the mechanism of which is as yet unexplained. It apparently has no lasting ill effect but may cause much discomfort to those severely affected. Paradione proved distinctly superior to Tridione in this respect. Only 13 per cent of patients of this selected group complained of photophobia when taking Paradione, against 33 per cent when taking Tridione. Patients would again suffer from photophobia when Tridione was substituted for Paradione, thus proving that accommodation to the dione was not responsible for the greater eye comfort of Paradione.

An infrequent side effect of the oxazolidine diones is lethargy. In contrast with the other symptoms, complaints were more frequent against Paradione (11 per cent) than against Tridione (4 per cent). The larger percentage of patients who complained of lethargy on Paradione is probably a reflection of its greater sedative action as demonstrated in laboratory animals.<sup>8</sup> No patients stopped medication because of this symptom, although it limited the dosages prescribed for a few children.

Nephrosis is a rare complication that has been reported but once in a patient taking Tridione.<sup>9</sup> One of our patients, a child of six, had petit mal seizures that were incompletely controlled with Tridione. Paradione was substituted and after a stormy period of prolonged petit mal status, seizures ceased. Some months later nephrosis developed and Paradione was discontinued without return of seizures.

## DISCUSSION

Comparison of these two drugs has shown that their over-all effects are similar, but some patients who fail to respond to one of them may be greatly improved by the other. The results for any given patient cannot be predicted beforehand, either from the duration or the type of seizures, or from the pattern of the spike and wave discharge in the electroencephalogram. For those who have grand mal associated with petit mal, Paradione seems to have the advantage of being less of a convulsant. A patient who experiences unpleasant side effects with one may have no difficulty with the other. If we could have but one of these drugs, the less toxic effects of Paradione probably would overbalance its somewhat smaller effectiveness and its greater cost. However, the individuality of response to medication and the urgent need for help are so great that physicians should, if possible, have access to both of the oxazolidine diones.

## CONCLUSIONS

In epileptic patients, Paradione seems to have less convulsive action than Tridione. The effect of the two drugs on petit mal was compared directly in seventy-three patients. In general, Paradione was no more effective in stopping petit mal than Tridione, but it caused much less photophobia and somewhat less neutropenia. The hypnotic effect was greater. Paradione proves either more effective or less toxic than Tridione in enough individuals that this drug should be available to physicians in their treatment of patients with petit mal.

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## STREPTOMYCIN THERAPY FOR PERTUSSIS

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THE use of streptomycin in treatment of twenty-seven patients with severe whooping cough significantly reduced the death rate of infants and small children. The death rate in a control group of twenty-eight patients was more than five times that of the treated group.

All discussions of pertussis stress the seriousness of this disease in the first six months of life. Fatality rates for this age group are variously quoted as ranging from 30 to 50 per cent.<sup>1, 2</sup> Over the age of 5 years the disease is rarely fatal. The mortality rate for the United States is 2.3 per cent and the case fatality rate in Arkansas for 1947 was 3.3 per cent.<sup>3</sup> If the case fatality in Arkansas by age groups is further analyzed, it is found that 40 per cent of the deaths occur in children under 3 months of age, 28.5 per cent in children under 4 to 6 months or 68.5 per cent in those under 6 months of age. Fortunately the invaluable contribution of McGuinness and associates,<sup>4, 5, 6</sup> in the development of hyperimmune human antipertussis serum has already given the physician a potent weapon with which to combat the disease. The use of antibiotic agents provides an additional means of therapy.

The studies in many investigators have indicated that streptomycin is effective against the *Haemophilus pertussis* in vitro. On the basis of these results this study of the clinical effect of the drug was undertaken shortly after the antibiotic was released from the control of the Committee on Chemotherapeutics of the National Research Council and has continued up to the present time.

No selection of cases was practiced since it was the policy to admit to the isolation wards of the University Hospital only severe cases usually with complications or infants under one year of age.

The criteria for establishing the diagnosis of whooping cough were as follows:

1. A positive culture for *H. pertussis* plus evidence of respiratory infection.
2. A respiratory infection characterized by paroxysmal coughing and leucocytosis with a definite increase in lymphocyte count plus any or all of the following supplementary factors:
  - A. History of pertussis in siblings or history of close contact with active cases.
  - B. Vomiting following paroxysms.
  - C. Characteristic whoop of recent onset.

Patients more than 8 months of age were admitted only if the disease was severe. Severity was judged by the presence of conjunctival ecchymoses, en-

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cephalopathy, dehydration resulting from severe vomiting or evidence of pneumonia. A diagnosis of pneumonia as a complication was based on physical findings, fever, x-ray of the chest, or all three combined. Pneumonia is the most common complication of whooping cough. It usually is found in most patients who die of pertussis. The following pathologic changes occur: scattered areas of consolidation, atelectasis, peribronchial infiltration with involvement of adjacent alveoli, and interstitial thickening of the alveolar walls.<sup>7</sup> In this study fourteen cases in the treated group and seventeen in the control group were complicated by pneumonia. Eight patients of the treated group and ten of the control group were under 8 months of age.

The patients who met the above requirements for diagnosis and had been admitted during approximately the three years prior to the advent of the streptomycin therapy were considered to be suitable for classification as control cases. By sheer chance, the number of these patients has been found to be practically equal to those who have received treatment to date.

Since we were aware of no published data to guide in determination of the dosage of streptomycin, it was decided to adopt the dosage recommended by the Committee on Chemotherapeutics of the National Research Council for treatment of *Haemophilus influenzae* meningitis. Accordingly, 25 mg. per pound of body weight was considered to be the total daily dose. The total dose was divided into eight equal parts and administered by the intramuscular route every three hours. The range of the number of days during which patients were treated with streptomycin was one to sixteen and the arithmetic mean of this range was seven days per patient. In most of the patients, treatment was continued for three to four days after the temperature was normal. Nineteen of the patients treated with streptomycin also were treated with sulfadiazine or penicillin or both for complicating secondary infection but without any noticeable improvement of the whooping cough. Sedation and oxygen therapy for cyanosis and control of paroxysms were used in both groups. In 1940 Kohn<sup>8</sup> reported thirty-three patients with pertussis pneumonia treated with sulfadiazine and noted no significant improvement in results other than had been obtained by supportive therapy alone. In our series, twenty of the control group received sulfadiazine or penicillin before the advent of streptomycin and results show a high death rate.

The number and severity of paroxysms were charted for each twenty-four hours, as was the frequency of vomiting and recurrent cyanosis.

Improvement was considered to be definite when the severity and number of paroxysms decreased, the infant was able to nurse, vomiting diminished, and cyanosis became less frequent. In the majority of instances, some improvement was noted within twenty-four to forty-eight hours as seen in Table I, and definite

TABLE I. DAYS REQUIRED FOR SIGNIFICANT IMPROVEMENT ACCORDING TO AGE DISTRIBUTION

NO. CASES	AGE DISTRIBUTION	RANGE	ARITHMETIC MEAN
19	0 to 8 months	0.5 to 10	3
4	8 mo. to 3 years	1 to 5	2.5
4	3 years and over	1 to 5	4

improvement occurred in three to four days. In three cases definite improvement was not noted until seven to ten days had elapsed. Positive cultures for *H. pertussis* were obtained in five of the twenty-seven cases. These five patients had been ill only one week prior to admission.

An analysis of the effect of streptomycin therapy on the number of days required for hospitalization revealed no significant difference between the treated and the control group as is shown in Table II. However, it is likely that the duration of treatment could be reduced by a day or two.

The difference in the case fatality rate is most striking. This is presented in Table III. The case fatality rate in the control group is 39.3 per cent and is 7.4 per cent in the treated group. The actual difference in fatality between the control and treated is 31.9 per cent. The standard error of difference between the two values for case fatality, namely control and treated groups, is plus or minus 10.5 per cent. In other words, the actual difference in case fatality in the two groups is slightly more than three times the standard error.

TABLE II. TOTAL HOSPITAL DAYS AND DAYS OF ILLNESS PRIOR TO ADMISSION TO THE HOSPITAL ACCORDING TO AGE DISTRIBUTION

AGE DISTRIBUTION	NO CASES	TOTAL HOSPITAL DAYS		DAYS OF ILLNESS PRIOR TO ADMISSION	
		RANGE	ARITHMETIC MEAN	RANGE	ARITHMETIC MEAN
0 to 8 months					
Treated	19	5-21	8	4-52	10
Control	13	1-28	7	6-42	14
8 months to 3 years					
Treated	4	2-17	6.5	5-35	21
Control	9	1-29	9	12-48	28
3 years and over					
Treated	4	9-16	12.5	4-25	14
Control	6	3-32	14	10-49	21.5

TABLE III. COMPARISON OF CASE FATALITY RATES OF VARIOUS AGE GROUPS OF TREATED AND CONTROL CASES

AGE DISTRIBUTION	NO CASES	TYPE OF CASE		RESULTS			
		SEVERE	COMPLICATED BY PNEUMONIA	IMPROVED	UN-CHANGED	DIED	
						NO.	%
0 to 8 months							
Treated	19	11	8	16	1	2	10.5
Control	13	3	10	6	0	7	53.8
8 months to 3 years							
Treated	4	0	4	4	0	0	0
Control	9	2	7	7	0	2	28.5
3 years and over							
Treated	4	2	2	4	0	0	0
Control	6	6	0	4	0	2	33.3
All ages							
Treated	27	13	14	24	1	2	7.4
Control	28	11	17	17	0	11	39.3

Standard error of difference  $\pm 10.5$ .

Actual per cent of difference in case fatality 31.9.

#### DISCUSSION

Although the number of cases presented is not great, it is felt that the controls represent a group similar to the treated group and that essentially the



two groups come from the same "universe." Because of this fact plus the significant results obtained, it is felt that it is justified to conclude that streptomycin in the dosage administered was of definite value in the reduction of the mortality in whooping cough, especially in the age group of 0 to 8 months and in those cases complicated by pneumonia, and that its effectiveness in clinical therapy of *H. pertussis* infection parallels its effectiveness against the organism in vitro and in experimental infection as suggested by Alexander.<sup>9</sup> In 1946 Alexander made the statement that the results of in vitro sensitivity tests provided an index of therapeutic effectiveness of streptomycin in *H. influenzae* meningitis and that the same in vitro tests showed that the range of sensitivity of *H. pertussis* was not significantly increased over that of *H. influenzae*. She stated at that time that there was reason to believe that streptomycin would prove an effective agent against *H. pertussis* infection but that clinical trial was inadequate for evaluation. In 1948 Coffey and Levy<sup>10</sup> reported six patients with pertussis pneumonia treated with streptomycin. Two of these patients died and four showed marked clinical improvement within forty-eight hours of the time that streptomycin therapy was started. The larger series presented in our paper accentuates the favorable results that may be expected.

Dowling<sup>11</sup> has reported that fourteen seriously ill patients under 7 months of age showed clinical improvement after receiving 25 mg. of streptomycin intramuscularly at three-hour intervals for five days. No statement was made regarding the occurrence of pneumonia as a complication. No difference in period of hospitalization was noted between the fourteen treated patients and twenty control patients of the same age group. No deaths were noted in either group.

Because of the need for numerous injections, streptomycin is necessarily a treatment for the hospitalized patient. Our results suggest that it should be used on the critically ill patients in addition to hyperimmune serum. Hyperimmune serum probably will continue to be of inestimable value in the treatment of the very ill patient who of necessity must remain at home.

Two newer antibiotic agents show promise of being effective in the treatment of pertussis. Swift<sup>12</sup> treated ten children aged one month to 2.5 years with aerosporin and noted beneficial results when treatment was started early in the course of the disease. Aerosporin is a product derived from the culture of *Bacillus aerosporus* Greer isolated by Ainsworth, Brown, and Brownlee.<sup>13</sup> This product was similar to, but not identical with, polymyxin obtained from filtrates of cultures of *Bacillus polymyxa* by Benedict and Langlykke<sup>14</sup> and by Stansly, Shepherd, and White.<sup>15</sup>

Polymyxin has been found to have a therapeutic effect against pertussis by Schoenbach, Bryer, Bliss, and Long.<sup>16</sup> According to Long, polymyxin has been found to comprise a mixture of antibiotic substances and refinements in production are still necessary. Long and his associates have found that polymyxin causes transitory renal damage in its present form.<sup>17</sup> Polymyxin is definitely more toxic than streptomycin at the present time.

So far as could be ascertained, no vestibular damage occurred nor were any other unfavorable reactions noted attributable to the use of streptomycin in our series of cases.

#### CONCLUSIONS

1. The use of streptomycin in a dosage of 25 mg. per pound of body weight caused a definite and rapid improvement of twenty-four patients with severe pertussis.

2. Comparison of the case fatality rate of the group of twenty-eight controls and twenty-seven treated patients revealed a statistically significant reduction in the treated group. The actual difference in the case fatality in the two groups is slightly more than three times the standard error.

3. No significant improvement in the length of hospitalization was noted in the treated group as compared to the control group.

4. Streptomycin in conjunction with hyperimmune serum should be used on all critically ill hospitalized pertussis patients.

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## ACCIDENTAL VACCINIA: REPORT OF TWO CASES IN INFANTS, WITH ECZEMA VACCINATUM IN ONE CASE

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**A**CCIDENTAL vaccinia is the condition which results from fortuitous contamination of a person with the virus of vaccinia by direct contact with smallpox vaccine or with an active lesion after smallpox inoculation. In view of the number of vaccinations that are performed, accidental vaccination occurs infrequently. Berggreen<sup>1</sup> in 1936 reported that between the years 1920 and 1935 only ten cases of accidental vaccination were observed at the Berlin Haut Polyklinik. A review of the literature revealed that the most frequent location of accidental inoculation is the region of the eyes. Since Jenner introduced vaccination for smallpox in 1796, approximately 100 cases of ocular complications from accidental contamination have been reported. The eyelids rather than the eyeballs are the usual sites of involvement. Less frequently the conjunctiva and cornea are involved. Disciform keratitis, resulting from accidental vaccinia has been reported recently by Brav.<sup>2</sup> Another less frequent location of accidental vaccination is the nasal region. In 1942, Ayo and Braley<sup>3</sup> collected from the literature sixteen cases of accidental vaccination of the nose. The face, tongue, fingers, and the external genital organs also may be sites of accidental inoculation.

Accidental vaccination usually occurs in nonimmunized persons who have come in contact with an active primary vaccinia. The spread is usually from a newly vaccinated sibling to a nonimmunized sibling or parent, or it may be from a newly vaccinated adult to a nonimmunized member of the family. However, there have been several cases of accidental vaccinia among laboratory workers who help to prepare vaccine. Horgan and Haseeb<sup>4</sup> reported a series of repeated accidental vaccinations among workers who possessed strong or complete vaccinal immunity.

As is well known, there may be three types of reactions to the usual inoculation for smallpox: (1) primary vaccinia or normal take, (2) an accelerated reaction, or (3) an immune reaction.<sup>5</sup> If the technique is faulty or the vaccine impotent, there may be no reaction. The primary vaccinia or normal take is the usual response of the nonimmunized person. This consists of the progressive development of a single papular-vesicular-pustular lesion at the site of the inoculation during a period of about two weeks. The papule develops by the third or fourth day after vaccination. The papule becomes a vesicle on about the fifth day. By the seventh day a red areola is present around the vesicle. During this time the vesicle becomes pustular. It is the discharge from such a vesicle that usually serves as the source for accidental

vaccination. By the seventh day after vaccination the vesicle begins to dry and the formation of a crust occurs. By the eighteenth day after vaccination the crust usually becomes detached.

An accelerated reaction is seen in persons who have been immunized previously but who do not have total immunity. The reaction is similar to that of primary vaccinia but the process is completed in a much shorter time, within eight or ten days. The crust is small and the scar is minimal.

An immune reaction occurs in those individuals who have been totally immunized against smallpox, either by having been previously vaccinated successfully or by having had smallpox. This reaction consists of the development of an area of redness at the site of inoculation within twenty-four to forty-eight hours after vaccination. A small papule may result but it does not progress to the vesicular stage.

The vesicle of the lesion due to accidental vaccination in the nonimmunized person usually appears from two to three weeks after the time of inoculation of the person from whom the accidental contamination has occurred. Therefore, it represents a primary reaction or a normal take. When vesicles of accidental vaccination develop within a shorter time after inoculation for smallpox, the reaction probably is of the accelerated type. Immune reactions probably occur in accidental vaccinations but the consequences are so slight that they may pass unnoticed.

Complications of primary vaccinia are many but occur infrequently. Probably the most common are the benign exanthemas and multiform eruptions that occur after vaccination. Bloch<sup>6</sup> reported that in 500,000 individuals vaccinated in Glasgow at the time of the 1942 smallpox scare, 123 had postvaccinal eruptions. None of these eruptions were classified as that of generalized vaccinia, that is, a disseminated vaccinal eruption. The majority of the eruptions were erythematous or urticarial in nature. There were a few purpuric reactions. Some were reported as pustular and some as eczematoid. The interval between the time of vaccination and the time of eruption in most cases was from seven to eleven days. Paschen<sup>7</sup> in 1932 gave an excellent classification of postvaccinal eruptions.

Autoinoculation is another complication which may occur. This probably is the most common cause of ocular complications after vaccination. One of the most serious complications of vaccination occurs when children who have eczema are vaccinated. This condition is known as "eczema vaccinatum." Lesions of vaccinia usually occur in the same locations as the pre-existing cutaneous lesions.

Most of the other complications of vaccinations are rare. Postvaccinal encephalitis was seen in the Glasgow smallpox scare in a ratio of 1:70,000 vaccinations.<sup>8</sup> Thompson<sup>9</sup> in 1931 reported an incidence of 1:12,000 to 1:330,000. Encephalitis usually occurs between the sixth to fourteenth day after vaccination. Myelitis,<sup>10-12</sup> neuronitis,<sup>13</sup> polyneuritis,<sup>14</sup> retinitis,<sup>14-16</sup> and orchitis<sup>17</sup> have followed vaccination. Infections of bones and joints with vaccinia also have been cited.<sup>18</sup> Tetanus<sup>19, 20</sup> and syphilis have been known

to develop from secondary infection of the vaccination. Both Schönlein-Henoch purpura<sup>21</sup> and thrombocytopenic purpura<sup>22</sup> have been reported after primary vaccinia and generalized vaccinia, respectively. Uncomplicated generalized vaccinia has been reported by Jubb<sup>23</sup> to occur once in 20,000 vaccinations. He reported the mortality rate from it as between 10 and 30 per cent. The mortality rate in eczema vaccinatum reported by McKhann and Ross<sup>24</sup> was 33 per cent.

Any of the various complications mentioned may occur with accidental vaccinations also. The most common are the ocular complications involving the eyelids, conjunctiva and cornea. The most serious are the cases of eczema vaccinatum. Riley and Callaway<sup>25</sup> reported two cases of eczema vaccinatum and reviewed the literature in 1947. In one of the two cases which we are reporting in this paper eczema vaccinatum occurred.



Fig. 1—Case 1 Accidental vaccination of right cheek of a male child 18 months old

#### CASE REPORTS

CASE 1.—A white male child aged 18 months was admitted to the Mayo Clinic and immediately hospitalized because of a large, single, pustular lesion on the right cheek. Nine days before his admission to the hospital both of his older sisters, aged 7 and 9 years, had been vaccinated for smallpox. Neither sibling had been vaccinated previously. The older sibling exhibited an immune reaction and the younger one demonstrated an accelerated reaction. Five days after the siblings were vaccinated, erythema developed on the patient's right cheek. This became papular and finally a pustule developed. An attempt was made to rupture this pustule with a needle. After this, the

lesion began to discharge seropurulent material. The day before admission the lesion was the size of a dime and had begun to crust. Seropurulent discharge exuded from beneath the crust. The region of erythema became larger, measuring 3 or 4 cm. in diameter, and involved the entire right cheek and eyelid. The right eye was swollen shut.

The child's rectal temperature at the time of admission to the hospital was 101.2° F. Physical examination revealed the lesion described with a few small secondary papules just below it. At this time the major lesion resembled that usually seen eight or nine days after vaccination for smallpox. Material from the lesion was cultured but results were reported to be negative. A positive Paul test<sup>26</sup> was not obtained. Values for hemoglobin and erythrocyte, leucocyte, and differential blood counts were normal. The edematous lesion was treated with moist compresses. Because it appeared to be secondarily infected and fever was present, 80,000 units of penicillin were administered intramuscularly each day as a precautionary measure. By the fourth day in the hospital the secondary infection had disappeared and the papule had a well-defined crust. The edema and erythema had disappeared and the lesion resembled that following vaccination for smallpox.

The child was dismissed from the hospital on the tenth day. Three months later the child was vaccinated against smallpox; there was no reaction. Eleven days later the child was revaccinated; forty-eight hours afterward there were definite signs of an immune reaction with redness, some induration, and three minute vesicles.

CASE 2.—A white male child aged 6½ months was brought to the clinic and was hospitalized immediately because of a severe skin disorder. The baby had first exhibited signs of eczema at 7 weeks of age. The eruption had started on the cheeks and had spread to the ears, forehead, and scalp. When he was 10 weeks of age the extremities had become involved. Numerous attempts had been made to control the eczema by dietary means without success.

The family history was not known. The child had been adopted at the age of 17 days. He had not been immunized against any contagious disease. However, his foster mother had been vaccinated fifteen days previously against smallpox and had had an accelerated reaction. Thirteen days after the mother's vaccination, pustules developed in the dry eczematous region above the baby's right eye and on his left cheek. The next morning the face began to swell. The entire face rapidly became similarly involved. He was admitted to the hospital about twenty-four hours later.

At time of admission the rectal temperature was 103.2° F. The entire face was covered with moist, bleeding, umbilicated pustules. The eyes were swollen shut. The anterior surface of the chest and abdomen were less markedly but similarly involved with umbilicated lesions. A diagnosis of eczema vaccinatum was made.

Cultures of material taken from the lesions on the face revealed hemolytic streptococci and *Pseudomonas*. The vaccinal virus was proved to be present by the Paul test. Penicillin in daily doses of 160,000 units was administered intramuscularly to combat the secondary infection. Elixir of phenobarbital and acetylsalicylic acid were employed as sedatives. The mother's blood was group A, which was unsuitable for the baby. Plasma, therefore, was extracted from the mother's blood and 20 c.c. of it were given intramuscularly each day to the child for the first three days.

During the first three days in the hospital the child's temperature taken by rectum varied from 102° to 105° F. On the fourth day it fell to 99° F. After

this, there was a secondary rise to 103° F. The temperature did not return to normal until the eighth day, after which time it remained normal until dismissal on the fifteenth day.

On admission the value for hemoglobin was 13.2 Gm. per 100 c.c. of blood. The erythrocyte count was 4,730,000 per cubic millimeter of blood. The leucocyte count was 14,300 per cubic millimeter; 17 per cent of these were lymphocytes, 14 per cent monocytes, 2 per cent eosinophiles, and 9 per cent filamented and 58 per cent nonfilamented polymorphonuclear neutrophils.



Fig. 2—Case 2. Eczema vaccinatum in a male child 6 months old

On the second day in the hospital the lesions on the face and forehead were confluent and pustular. There were scattered discrete lesions on the chest, abdomen, and extremities. Mild antiseptic packs were applied. By the third day after admission, most of the pustules on the face had ruptured. The face exhibited a reddish, moist appearance. By the fourth day the lesions on the trunk were drying and there was further improvement. At this time the leucocyte count had dropped to 9,000 cells per cubic millimeter of blood. Urinalysis revealed nothing abnormal. One week after admission mild topical ointment was applied to the healed lesions. The child was dismissed two weeks after admission. There was no scarring of the face on dismissal.

#### COMMENT

In Case 1, the accidental vaccinal reaction which occurred on the child's right cheek appears to have been of the accelerated type because it developed to a papular stage within five days after the siblings had been vaccinated. The lesion no doubt had been secondarily infected at the time it had been ruptured

with a needle. This probably shortened the period between the vesicular and pustular stages. The secondary infection and the precarious location near the right eye were the gravest factors in this case. In spite of the considerable inflammatory reaction with edema of the eyelids, the bulb of the eye was not involved. Although a positive Paul test was not obtained in this case, an active immunity to smallpox apparently developed from this accidental vaccination, as was proved by the immune reaction which followed vaccination for smallpox three and one-half months later.

In Case 2, an eczematous infant was accidentally inoculated with vaccinia as a result of contact with the vaccination of his foster mother. The time interval of thirteen days between the mother's vaccination and the appearance of the baby's lesion showed that the child possessed no immunity and would probably have had a single lesion of primary vaccinia if he had not had the eczematous condition. The hypersusceptibility of persons who have cutaneous disease to the vaccinia virus is striking. This may be related to an allergic reaction, which has been suggested by various authors,<sup>27-29</sup> particularly in the development of generalized vaccinia. The rapid toxic reaction which the second patient showed could be due also to the effect of the secondary hemolytic streptococcal infection. This infection was brought under control with penicillin and antiseptic compresses. Passive immunity to vaccinia was attempted by giving the mother's plasma to the child.

Positive proof that vaccinia was the source of this condition was shown by a positive Paul test. This test consists of inoculating the scarified eye of a rabbit with the seropurulent material from the lesion. Within thirty-six hours the rabbit's cornea will show definite changes if the vaccinia virus is present. Fixation of the enucleated eye for one minute in a solution of 2 parts of 6 per cent mercury bichloride and 1 part dehydrated alcohol causes the isolated, intensely white, opaque elevations to be seen on the cornea. Histologic section through this part of the cornea may show Guarnieri bodies which are thought to be specific for the vaccinia virus. A positive result of the Paul test is considered pathognomonic for smallpox and is useful in differentiating this condition from other virus infections, particularly varicella.

The spread of vaccinia from the initial site of inoculation, accidental or otherwise, is considered to be by way of the blood stream.<sup>30</sup> It has been demonstrated that within four or five days after vaccination, the vaccinia virus may be present in the nasopharynx and that dissemination through the body is hematogenous.<sup>31</sup>

As was seen in Case 1, active immunity developed from accidental vaccination. No attempt was made to revaccinate the eczematous child in order to prove his immunity. Busch<sup>32</sup> reported a case in which a boy had two attacks of eczema vaccinatum within a period of four years. The second attack was fatal. The presence of severe secondary infection rather than the direct effect of the vaccinia virus may have caused the death. If total immunity had been developed by the primary attack, the second attack of eczema vaccinatum would not have developed.



In the literature there has been considerable discussion concerning the relationship of *eczema vaccinatum* and Kaposi's varicelliform eruption. Tedder<sup>33</sup> in 1936 and Ronchese<sup>34</sup> in 1943 stated that *eczema vaccinatum* and Kaposi's varicelliform eruption seemed to be identical conditions. Although both occur among persons who have *eczema*, recent evidence indicates that Kaposi's varicelliform eruption is due to the virus of herpes simplex. Lane and Herold<sup>35</sup> in 1944 stated that the two conditions can be differentiated. Hershey and Smith<sup>36</sup> in 1945 concluded that the vaccinia virus and the herpes virus are capable of producing similar eruptions in the skin of *eczematous* children. Several reports<sup>37-39</sup> have been made of cases of small epidemics of Kaposi's varicelliform eruption which clinically resembled *eczema vaccinatum*, but in which there was no history of vaccination or contact with a recently vaccinated individual. In these cases herpes simplex virus was found.

Barton and Brunsting of the Mayo Clinic reported two cases of Kaposi's varicelliform eruption associated with *eczema* in which the herpes virus was isolated. Their patients were adults. Kaposi's varicelliform eruption, as well as *eczema vaccinatum*, is attended with a high mortality rate. Among children less than 3 years of age it is more than 50 per cent.<sup>40</sup>

The diagnosis of accidental vaccination depends on the clinical history and certain laboratory findings. There should be a history of vaccinal contamination within a period of two or three weeks before the onset of symptoms. The lesion or lesions should resemble those of primary vaccinia and should pass from the papular to the vesicular and pustular stages. Biopsy of an individual lesion may show Guarnieri bodies. The Paul test is the most reliable laboratory procedure. Serologic methods for the determination of antibody formation against the vaccinia virus have been devised<sup>41</sup> but as yet they are impractical for general use.

Virus infections, particularly infection with the viruses of herpes simplex and vaccinia, are hazardous to *eczematous* individuals, especially children. The dangers of accidental vaccination must be kept in mind as an important untoward result of vaccination. Caution should always be taken to protect nonimmunized individuals, particularly *eczematous* infants, from becoming accidentally vaccinated from the vaccinal lesion of a recently vaccinated person.

#### SUMMARY

The two cases of accidental vaccinia presented in this paper consist of (1) a case of uncomplicated inoculation of the cheek of a child 18 months old and (2) a severe case of *eczema vaccinatum* in a child 6½ months old. Both children recovered. The complications of vaccination are many but occur infrequently. Probably the most common are benign exanthems and multiform eruptions. Accidental vaccinia may result from vaccination. One of the most serious complications of this is the development of *eczema vaccinatum* in an *eczematous* child. The relationship between *eczema vaccinatum* and Kaposi's varicelliform eruption is reviewed. The two cases reported indicate the dangers

of accidental vaccinia and make clear the need for protection to prevent the accidental vaccination of nonimmunized individuals by a recently vaccinated person.

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# EVALUATION OF REPLACEMENT TRANSFUSION IN THE TREATMENT OF HEMOLYTIC DISEASE OF THE NEWBORN INFANT

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LATE in 1941 the clinical importance of the Rh factor in isoimmunization in pregnancy and sensitization by incompatible Rh transfusions was recognized, and it was established that hemolytic disease of the newborn infant (erythroblastosis fetalis) was the result of this antigen-antibody reaction. Since that time many of our best serologists have worked ardently on the subject, and it is due to their zeal that this complicated condition has been clarified in so short a time.

No subject could advance at such a pace without the evidence of differences of opinion. This is true of the serologic aspect of the subject, and today there are divergent views concerning the proper treatment of infants afflicted with hemolytic disease of the newborn.

For twenty-years I have treated icterus gravis by means of multiple transfusions.<sup>1</sup> During this period it became apparent that some of the infants were saved, but the severe cases died.

In 1942 when it became evident that the Rh factor was clinically important, we started using Rh-negative blood and multiple transfusions. As the subtypes of Rh were determined and the Hr setup recognized we used homozygous Rh-positive blood in transfusing these rare Hr cases. With this regime there was a definite improvement in our results, but there was still much left to be desired.

For the last two years we have been treating our patients with severe cases of hemolytic disease of the newborn infant by means of replacement transfusion.

The manner in which erythroblastosis manifests itself is often baffling. It is not always easy, even with meticulous history, perfect cooperation with the serologist, and careful physical examination, to make an early diagnosis or to evaluate just how severely affected a child may be and thus foretell the probable outcome. Undoubtedly, some cases are mild and the infants recover unrecognized. Some infants appear perfectly normal at birth or for the first twenty-four hours of life, and are dead of hemolytic disease in two to three days. Severe erythroblastosis, however, is often easily recognized at birth or shortly after, when it is seen that the baby is in grave trouble: the child may be convulsive or in shock, showing rapid, difficult respirations, weak cardiac action, petechiae and cyanosis, through which jaundice and probably anemia begin to appear. When the child is examined an enlarged but soft spleen and liver are found. The blood shows more or less erythroblastosis and anemia, and the red cells show sensitization which is demonstrated by their agglutination with normal compatible adult serum. The Witebsky-Rubin test is a very important aid in diagnosis,<sup>2, 3</sup> this agglutination phenomenon can also make the blood of these babies difficult to type, and because of this, it is probably safer to use O blood

ERYTHROBLASTOSIS  
No. 1, 2, 3, 4, to be filled out  
by the Obstetrician

1) History (With Dates)  
Pregnancies

History of Transfusions

2) Blood Typing

R. H.

A. B. O.

3) Examination of Mother's  
Blood (Antibodies) with  
Dates

4) Birth  
(Leave Long Cord)

5) Cord Blood  
To Laboratory

6) Physical Examination of  
Baby (Frequently) Dur-  
ing the First Few Days

7) Treatment  
Replacement  
Transfusion  
Blood Type Given

8) Results of Agglutination  
Tests Taken During  
Transfusion

9) Results

CHART SHOULD BE FILLED OUT WHEN  
ERYTHROBLASTOSIS IS SUSPECTED

Aberrances	Normal	Viable Births Jaundiced	Total Pregnancies	Condition of Infant at Birth	Final Appraisal of Off-spring
RHI + or RII - Blood Used?					
Mother		Father	Wassermann	Siblings	
Date	Hour				
Date	Hour	Remarks Concerning Delivery, etc.			
Hg. Gms.	Type	RII	Erythroblasts Per 100 W.B.C.	Ict. Index	Antibody
Day and Hour	Jaundice	Cyanosis	Petechiae	Spleen	Liver
Umbilical	Type	Saphenous	Time	Blood, C.C. Withdrawn	Blood C.C. Given
Witebsky-Rubin Test		Coombs	RII	Condition Following Transfusion	
Date	Hg (Gm.)	Erythroblastic Count per 100 W.B.C.	Icteric Index	Physical Examination	

with added A B substance when transfusing patients with hemolytic disease of the newborn infant. A diagnosis or prognosis is not made on a single sign or symptom; account *must* be taken of the case as a whole.

Chart 1 is a sample chart for recording cases of erythroblastosis.

Many patients are dead at birth or are so severely affected that no known method of treatment can save them. In severe cases we believe early diagnosis and early replacement transfusion is the treatment of choice and will result in saving the lives of many who would otherwise be sacrificed. We do not believe in reserving this measure for cases in extremis; if this were done there could be no basis for comparison of treatments. Comparative statistics concerning treatment in erythroblastosis are at best difficult of evaluation.

Clinical classification of hemolytic disease of the newborn infant is difficult and there appears to be no connection between the type of antibody and the clinical manifestation of the disease. Occasionally there is no correlation between the serologic and hematologic findings and the clinical picture. We have seen severely affected babies born when the discernible antibodies in the mother were absent or low\* and occasionally have seen high maternal antibodies and a child unscathed in spite of his being of susceptible Rh-positive type.

Because of these incongruities we believe that replacement transfusion should be done on the babies whose families have a history of marked sensitization and who are shown serologically and clinically to be suffering from hemolytic disease of the newborn infant.

A woman who is sensitized remains so, and when she has given birth to an erythroblastotic child practically all subsequent susceptible offspring will be affected in increasing severity. Chown's<sup>4</sup> report on a series of normal susceptible babies following the birth of erythroblastotic babies is the exception to the rule for which we have no explanation. We have observed such cases.

It has been stated that the evaluation of treatment should be based on a statistical study of 1,000 cases, treating alternate cases by means of either multiple transfusions or replacement transfusion. Who would have the audacity to institute such a regime or the longevity to complete such a statistical study? (A compilation of statistics from different clinics would not be satisfactory for comparison.) I would just as soon take 1,000 cases of appendicitis in childhood, operate on every other patient, then observe my results for science. Zuelzer, Wheeler, and Leonard<sup>5</sup> have endeavored to establish the severity of erythroblastosis by the evaluation of signs and symptoms and combinations of these. They have correctly pointed out that a diagnosis or prognosis cannot be made without a careful study of the case as a whole. This is a difficult assignment and because of the exceptions which occur, early estimation concerning the degree of sensitization and forecast of the clinical severity of the disease is sometimes impossible. It is important, however, in determining the kind of treatment to be used.

\*The failure to find antibodies is not as common since the incomplete anti-Rh antibody was recognized, and there are probably antibodies still to be discovered. Antibody titer is best determined by saving the blood samples of the mother taken throughout pregnancy and comparing them at one examination toward the end of pregnancy. Slight differences in dilution and agglutination make a marked difference in antibody titer reading. (Witebsky.)

At present only the severe types of the disease are being referred to us for replacement transfusion. In 1947 we lost the first two patients out of a total ten cases. One died of a severe hemolysis due to overheated blood: the other was in extremis, dying during replacement; this infant had received a previous ordinary transfusion. Both of these cases were mistakes. Doing a replacement transfusion after ordinary transfusion always is hazardous and probably should not even be attempted. In the remaining eight cases, all severe, the infants recovered and today are alive and well and show no discernible neurologic sequelae.

During 1948 we have done replacement transfusions on sixteen patients and lost three; the three losses were last ditch attempts to save the lives of babies who were so severely damaged at birth as to preclude any kind of successful treatment. Thus in 1947 and 1948 we report a mortality of 19.2 per cent in our severe cases treated by replacement transfusion. We have broken down our mortality statistics and report on thirteen patients who were proved to have had erythroblastotic siblings; these patients treated by replacement transfusion showed a mortality of 15.3 per cent. This figure indicates the severity of the whole series treated by replacement, the mortality of the whole series being 19.2 per cent. We realize this is not a large series of cases from which to draw statistical evidence. All our fatal cases have been posted; the findings were those of severe erythroblastosis. There was no incidence of air embolism. One case showed massive cerebral hemorrhage.

Most of our cases treated by replacement transfusion are severely affected. As an example I quote the case of B.M.K. whose mother's history is as follows: She had a normal child born in 1941, a stillbirth in 1942, and in 1944 had an abortion at the third month. The mother was never transfused (abortions and transfusions play an important role in immunization). Bruce was the result of the fourth pregnancy, normal delivery. He was born on January 5, 1948, and was jaundiced at birth, cyanotic, had petechial hemorrhages, and was in shock. The mother was O, Rh negative, the father O, Rh positive subtype Rh<sub>1</sub> Rh<sub>2</sub>. The baby's cord blood was Rh positive and showed the incomplete anti-Rh antibody in titer 1:128; the red cell agglutination with normal adult serum was strongly positive (4 plus). The icteric index was reported over 40, the Van den Bergh showed the prompt reaction 1.8 mg. per cent. The hemoglobin was 16 Gm., erythroblasts 42 per 100 leucocytes. The mother had anti-Rh saline agglutinins in her serum up to 1:2, and anti-Rh incomplete antibodies of at least 1:1024. The results of specimens taken during exchange transfusion were as follows: (1) agglutination of baby's cells in normal adult serum, positive up to the thirteenth specimen; (2) agglutination by anti-Rh serum on the slide, positive up to the fifteenth specimen; (3) Coomb's test strongly positive up to the fifteenth specimen, weak agglutination up to the 27th, and faint agglutination in the twenty-ninth specimen (29 specimens obtained). The report was by Dr. Ernest Witebsky. These tests are conclusive evidence of the completeness of the replacement.

In this case we were dealing with a severely sensitized child with high anti-Rh antibodies. The hemoglobin was not reduced and there was only a moderate

increase in erythroblasts. A 500 c.c. replacement transfusion was done. From our past experience it is difficult to believe that repeated transfusions without withdrawal and replacement could have possibly saved this baby's life. This type of treatment also avoids the danger of overloading the baby's circulation. The giving of too much fluid of any kind in these cases is a real hazard and extremely dangerous.

In our treatment of all cases of erythroblastosis we are very careful to correct existing dehydration, acidosis, hypoglycemia, hypocalemia, hypoproteinemia, hypoproteinemia, anemia, and anoxia.

All of the early blood specimens withdrawn in our replacement transfusions fail to clot; this shows grave abnormality in the clotting mechanism in cases of erythroblastosis fetalis. The blood is far from normal in *every* respect. Dr. Diamond aptly puts it: "Are you going to drain the crank-case of bad oil and replace it, or are you merely going to add a little new oil to the old bad stuff?" In the evaluation of replacement transfusion it can be stated that to a great extent it helps to rid the infant's blood of offending anti-Rh antibodies. It replaces its red cells which cannot be functionally good with red cells which cannot be acted on by the antibody, and are good oxygen carriers. The exchange relieves anoxia and probably tends to minimize liver and brain damage. Because of the withdrawal, this procedure does not overload the circulation and this is important when the blood volume is not low. I have seen patients die with a high hemoglobin without dehydration; this, however, is the exception.

Replacement transfusion has been done by various men<sup>6, 7, 8, 9, 10, 11, 12, 13, 14</sup> using different techniques. We use the umbilical vein method as described by Louis K. Diamond; this method should be used only the first twelve hours of life; at times the vein may be patent after twelve hours, but if used later there is the danger of disengaging clot and causing embolism. In replacement transfusion the giving of blood is easy; the difficulty is the withdrawal. Wallerstein<sup>7, 8</sup> used the longitudinal sinus for withdrawal and Wiener<sup>10, 11, 13</sup> withdraws from the radial artery using heparin.

Because of the bleeding tendency and poor clotting power of the blood in erythroblastosis fetalis, we believe the use of heparin in the child's circulation is not without danger.

When we do not use the umbilical vein, we withdraw and replace through the saphena magna vein using polyethylene tubing, gauge 18 and 19; these plastic catheters were developed by Dr. Frane Ingraham and used in umbilical vein replacement by Dr. Louis K. Diamond. The technique of the saphenous method is not difficult, it is neat and expeditious, and heparin is unnecessary. We prefer this technique.

Replacement transfusion is not radical treatment; it is conservative and, when properly done, holds practically no hazard. We have never had a case of air embolism. With proper technique this should not occur. Any kind of treatment or no treatment at all is hazardous in moribund or neglected cases of hemolytic disease of the newborn infant. In a last-minute effort to save a life, infants have died on the way to the operating room or shortly after starting



replacement. However, enough severe cases are saved to warrant doing a replacement transfusion and thus giving the baby a chance for life even though such a regime plays havoc with statistics.

In conclusion, it is readily seen that in handling cases of hemolytic disease of the newborn infant it takes good judgment based on fact in order to arrive at an early diagnosis resulting in effective early treatment.

Having used the various described treatments throughout the years, and having observed to date the concomitant use of the other methods, we have come to the conclusion that all severe cases of erythroblastosis fetalis should be treated by replacement transfusion. Only the mild cases can be temporized with, and some of the apparently mild cases turn out to be severe enough to cause death or result in brain damage. In case of doubt as to the severity of the immunization, we believe the baby should be given the benefit of the doubt and receive replacement. We are watching with interest the development of hapten or some other agent to prevent the deleterious action of antibody on the fetus and child.

This is not an exact controlled, statistical study. I do not believe this condition lends itself to such a statistical approach. This is, however, a study based on a twenty-two year observation of many cases of hemolytic disease of the newborn infant.

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# TICK PARALYSIS IN THE EASTERN UNITED STATES

## A SUMMARY, WITH REPORT OF FOUR NEW CASES FROM GEORGIA

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### INTRODUCTION

FOR many years tick paralysis has been recognized in the Canadian and American northwest, but only in the past decade have case reports begun to appear from the eastern United States. Though uncommon, the disease is important since it may be confused with poliomyelitis and, if unrecognized, may be fatal. The diagnosis is often readily confirmed by finding an engorging tick and by prompt recovery of the patient after its removal.

In the summer of 1948 four patients with tick paralysis were observed at Grady Memorial Hospital. These cases are being reported to emphasize an unfamiliar hazard in the eastern United States. Reference is also made to fourteen other published cases which have occurred east of the Mississippi River. Only a brief description of the disease is included since two excellent reviews<sup>1, 2</sup> are available.

### CASE REPORTS

**CASE 1.—History:** B. D., a 3-year-old white farm girl from Hazlehurst, Ga., was admitted May 13, 1948. She was well until two days before admission when she had three loose stools. Next day she got up in the morning but soon returned to bed. A little later she was unable to walk. She could move all extremities, but fell on attempting to stand. In the afternoon she became unable to sit up or raise her head. During the night she was irritable and hypersensitive, screaming when touched. The legs were weak and the right arm paralyzed. On the morning of admission she could still move the legs and left arm slightly. Her speech was indistinct and she choked on attempting to swallow. The choking became worse and breathing difficult. She lost consciousness just before entering the hospital at 3:00 P.M.

**Physical Examination:** The child appeared moribund. She was limp, comatose, drooling, and choking on pharyngeal secretions. The rectal temperature was 98.2° F., pulse 130, respirations 28. Breathing was shallow and diaphragmatic. The limbs were flaccid and motionless. Tendon and abdominal reflexes were not obtainable. There was little if any stiffness of the neck. Slight lateral nystagmoid movements of the eyes were noted. The nose and pharynx contained mucoid secretions, and the gag reflex was absent. A search of the scalp and body for ticks revealed none.

**Course:** The nose and pharynx were aspirated frequently, the foot of the bed elevated, and the head turned to the side. Oxygen was given nasally. Penicillin was administered intramuscularly, 40,000 units every six hours. Parenteral fluids were given. By 6:00 P.M. consciousness had returned and the speech, though thick and nasal, was comprehensible. During the night she could move all extremities, but there was marked weakness. She was unable to turn in bed, and when lifted the head fell back limply. The respirations

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became deeper and easier. On May 14 she could move her limbs better but the neck muscles were still weak. The knee jerks were present. Speech was normal and pharyngeal secretions gradually ceased accumulating. On May 15 the gag reflex had returned and she could take fluids by mouth. The respiration was normal and she was able to sit up. Weakness of the hands and neck flexors was still noted, but gradually subsided. All motor power quickly returned. On May 16 she was walking about in bed, and by May 17 recovery was complete.

There was no fever. No sensory loss was detected. Except for incontinence of urine during the first twenty-four hours of hospitalization, the bladder and bowel functioned normally throughout. The child was well when discharged on May 20.

*Pertinent Laboratory Data:* On admission the leucocyte count was 13,280 with 81 per cent polymorphonuclears, 16 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. The Kahn test was negative. Lumbar puncture on May 14 revealed clear fluid containing 4 lymphocytes per cubic millimeter, with 14 mg. of protein and 62 mg. of sugar per hundred cubic centimeters. The Pandy test was negative, and there was no growth on culture.

*Comment:* The initial impression was poliomyelitis. However, the absence of fever, the minimal stiffness of the neck, and the normal spinal fluid, combined with the extraordinarily rapid recovery, seemed to weigh against this diagnosis. The nature of the disease remained a mystery until the parents came to take the child home. It was then learned that on May 13 an engorged tick had been found attached to the scalp above and behind the right ear. It was removed by the parents at about noon, three hours before admission. This information, together with the typical clinical picture, established the diagnosis of tick paralysis.

The tick removed from the patient was not preserved, but several days later the father sent us six ticks collected from dogs at the child's home. These were identified as females of *Dermacentor variabilis*. One was unengorged and five were in various stages of engorgement. Some of them deposited large numbers of ova.

*CASE 2.—History:* V. C., a 4-year-old white girl also from Hazlehurst, Ga., but living some miles away from the patient of Case 1, was brought to the Emergency Room May 28, 1948, because of difficulty in walking. She was well until the morning of May 27 when she showed poor control of her legs and an unsteady gait. This improved somewhat toward evening but was worse on the morning of May 28. There was marked weakness and ataxia of the legs. The child was unable to walk without support, but paralysis was never complete. At 9:00 A.M. the parents found and removed two ticks, one large and one small, which were attached to the scalp in the right occipital region. On arriving at the hospital about 7:30 P.M. she had already improved considerably. There had been no fever.

*Physical Examination:* The child was alert and could walk, although the gait was unsteady with a wide base. The rectal temperature was 99.2° F. There was no stiffness of the neck or back. The cranial nerves were normal. All extremities could be moved, and there was little or no detectable muscle weakness. The upper abdominal reflexes were present, the lower ones were not obtained. Knee jerks were absent. Ankle jerks were present and equal. Bite marks were visible on the scalp where the ticks had been attached.

*Comment:* A diagnosis of tick paralysis was made from the history and the finding of ataxia of the legs with absent patellar and lower abdominal reflexes. The parents were allowed to take the child home without further treatment.

*CASE 3.—History:* F. D., a 6-year-old Negro girl from Lexington, Ga., was admitted to the hospital June 15, 1948, because of difficulty in walking. She

was well until the evening of June 12 when she seemed "feverish." On the morning of June 13 she was "weak in the knees" and could not walk. She complained of "stomach-ache" and had three loose bowel movements. Later in the day the gait was unsteady but she was able to walk about by holding on to objects. On June 14 the legs were still weak though not entirely paralyzed. She could not climb onto her tricycle, but was able to pedal it when placed on the seat. She fell on attempting to get off. At 11:00 A.M. she was seen by a physician who found her unable to stand and suspected poliomyelitis. She was admitted to the hospital at 11:00 A.M. June 15. Meantime some improvement had occurred.

*Physical Examination:* The child did not appear acutely ill. The rectal temperature was 100° F. She was able to stand alone, but the Romberg test was positive. She could walk with an unsteady gait on a wide base. There was no grossly detectable weakness of the extremities, but the knee and ankle jerks were absent. The plantar responses were flexor. Tendon reflexes in the arms were brisk and abdominal reflexes were normal. The neck was supple, Kernig's sign negative. A partially engorged tick was found attached to the scalp in the left temporal region. It was removed at 12:30 P.M. June 15.

*Course:* By the morning of June 16, twenty-two hours after removal of the tick, the child's gait had improved but was still slightly ataxic. The Romberg sign was negative. The left ankle jerk was obtainable with reinforcement. The right ankle jerk and both knee jerks remained absent. On June 17 the gait was normal. The left ankle jerk was easily obtained, the right was weakly present with reinforcement and improved slightly by the next day. On discharge June 18, the child appeared well but the knee jerks were still absent and the right ankle jerk was weaker than the left. There was no fever during hospitalization.

*Pertinent Laboratory Data:* On admission the leucocyte count was 9,200 per cubic millimeter with 52 per cent polymorphonuclears, 46 per cent lymphocytes, and 2 per cent monocytes. The Kahn test was negative. Lumbar puncture yielded a clear colorless fluid containing 1 leucocyte per cubic millimeter, with protein 12 mg. and sugar 56 mg. per hundred cubic centimeters. No growth was obtained on culture of the fluid. The tick was identified as a female of *D. variabilis*. Several days after removal it deposited a large number of ova.

*CASE 4.—History:* C. H., a 2-year-old white boy from Monroe, Ga., was brought to the hospital July 3, 1948, because of difficulty in walking. He was well until two days before admission when he became irritable and began walking "as though drunk." He cried whenever his legs were moved and preferred to lie quietly. Next day the legs were weaker; he was still able to stand and walk a few steps although use of the legs seemed painful. A physician found the temperature to be 101° F. rectally, suspected poliomyelitis, and the boy was admitted to the hospital at 9:00 P.M. July 3.

*Physical Examination:* The child was husky, with long curly hair. He resented being disturbed and screamed loudly during the examination. It was impossible to tell whether this was due to pain or apprehension. There was no stiffness of the neck. Kernig's sign was negative. Cranial nerves and upper extremities were normal. Generalized weakness of the legs was noted, without complete paralysis of any muscles. The child could stand alone, though weak and wobbly; the gait was unsteady with a wide base. The Romberg sign was positive. Biceps, triceps, and abdominal reflexes were present and equal bilaterally. Knee and ankle jerks were absent. The plantar responses were normal. Sensory examination was unsatisfactory but revealed no anesthesia. A partially engorged tick was found attached to the scalp in the occipital region, and removed.

*Course:* On July 4, twelve hours after removal of the tick, the child was much less irritable. He sat up well but the Romberg sign was still positive. The gait continued to be jerky and unsteady with a wide base. He cried while walking as though in pain. Knee jerks were present. On this day (one of the hottest of the summer with air temperature nearly 100° F.), he took fluids poorly and his rectal temperature rose to 101° F. There was no evidence of infection. On July 5, thirty-six hours after the tick's removal, some diffuse weakness of the legs remained. All tendon reflexes were present, equal, and hyperactive. The maximum rectal temperature was 100.2° F. On July 7, three and one-half days after removal of the tick, the child did not yet walk willingly. His gait, though improving, was still unsteady with a moderately wide base. Upon the insistence of his parents he was discharged from the hospital July 7. A physician later wrote that recovery was complete.

*Pertinent Laboratory Data:* The blood leucocyte count on July 4 was 15,200 with 53 per cent polymorphonuclears, 44 per cent lymphocytes, 1 per cent monocytes, and 2 per cent eosinophiles. On July 5 the leucocyte count was 12,100. The Kahn test was negative. Lumbar puncture on admission revealed clear fluid containing 2 lymphocytes per cubic millimeter, with 20 mg. of protein and 68 mg. of sugar per hundred cubic millimeters. Pandy test on the spinal fluid was negative, and culture yielded no growth. The tick removed from the patient was identified as a female of *D. variabilis*.

#### ETIOLOGY

Various species of Ixodidae or hard ticks have been reported to cause paralysis. The Argasidae or soft ticks have not been implicated. While engorging on its victim, the tick apparently injects a neurotoxin. This toxic agent is thought to act upon the spinal cord and bulbar nuclei,<sup>2</sup> causing incoordination, weakness, and paralysis. Evidently it is rapidly destroyed or excreted, for when the tick is removed the nerve cells regain normal function.

Tick paralysis has been produced in experimental animals only with gravid female ticks, and this observation led to the theory that the toxin was elaborated by the ova. While various toxic extracts have been prepared from tick eggs, the toxin causing paralysis in naturally occurring cases has not yet been definitely identified.<sup>4-6</sup>

It appears that the tick must feed for several days before symptoms develop. Paralysis has occurred in infants after a tick has engorged for four days, and various studies indicate that large amounts of toxin are injected on the fifth and sixth days.<sup>1</sup> Female ticks may feed on a suitable host for periods ranging from four to ten days or more, usually seven to nine. Paralysis becomes evident in experimental animals after five to seven days of engorgement.<sup>3, 7, 8</sup> Male ixodid ticks engorge to a lesser degree and feed for a shorter period. It has been suggested<sup>1a</sup> that this may explain why the female is more effective in producing paralysis. At least one case is on record, however, of paralysis caused by a male *D. andersoni*.<sup>9</sup> The tick was attached in the axilla of an adult, causing partial paralysis of the arm on the same side. This cleared within twelve hours after the tick's removal.

Since the salivary glands of ticks enlarge enormously while feeding, it has been postulated<sup>3</sup> that the toxin is present in the saliva and is introduced into the host in increasing amounts during the final stages of engorgement. Tick salivary glands were injected into animals with unconvincing results. Other

workers<sup>10</sup> were unable to produce paralysis with salivary gland extracts. In some human cases paralysis has continued to progress despite removal of the tick and improvement did not begin until broken-off mouthparts were excised.<sup>10, 11</sup> Such instances suggest that the mouthparts contain a high concentration of toxin. The nature of the toxin is still unknown. It is not clear whether it is formed in the salivary glands, or whether the saliva simply transmits or perhaps also activates a toxin formed in the ova or elsewhere.

#### CLINICAL PICTURE, TREATMENT, AND PROGNOSIS

Most human cases occur in children, especially in young girls. The tick is usually attached to the scalp and hidden by the hair. Both white and Negro races are susceptible.

Irritability may be noted twenty-four hours before appearance of motor symptoms. Mild diarrhea may occur. Often the first alarming symptoms appear in the morning when on arising the child shows weakness and poor control of the legs, staggering, and falling. Sensory changes are usually absent, but there may be hyperesthesia and paresthesia in the affected extremities. Flaccid paralysis soon develops and ascends in one or more days to involve the trunk, arms, neck, tongue, and pharynx. Tendon reflexes are diminished or absent. If the trunk is affected the abdominal reflexes are also unobtainable. There is little or no stiffness of the neck and back. With the appearance of bulbar involvement the voice becomes thick and nasal; the child is unable to swallow and chokes on pharyngeal secretions. Nystagmus and strabismus are sometimes noted, and in infants terminal convulsions may occur. The respirations become abdominal in type, shallow, rapid, and finally irregular. Restlessness gives way to stupor and death results from paralysis of the respiratory muscles or from respiratory obstruction by aspirated material.

The temperature seldom exceeds 100° F. unless there is a secondary infection. The leucocyte count is usually normal, although a leucocytosis of 10,000 to 17,000 cells per cubic millimeter is occasionally observed.<sup>12-15; see also Cases 1 and 4</sup> The spinal fluid is almost always normal. The erythrocyte count, hemoglobin, and urine show no changes.

If the tick is removed before appearance of bulbar signs, the paralysis subsides and recovery is complete within a few days. Milder cases may be quite well within twenty-four hours. Nevertheless all patients should be observed carefully until recovery is well under way, because if other ticks or retained mouthparts have been overlooked the paralysis may progress. When bulbar or respiratory paralysis develops, death may occur if the tick is not removed in time.

The tick is usually located on the scalp or neck, but may be attached to any part of the body, especially the ear, axilla, groin, vulva, or popliteal space. It should be removed immediately, with care to avoid breaking off the mouthparts and allowing them to remain embedded in the skin. Mouthparts which have been retained should promptly be excised. The whole body surface should be searched for other ticks.

In advanced cases respiratory and bulbar paralysis dominate the picture. If the patient cannot swallow and is choking on pharyngeal secretions, the

foot of the bed should be elevated and the head turned to the side to promote postural drainage. Frequent aspiration of the pharynx should be performed. Nothing should be given by mouth until the patient is able to swallow normally. Parenteral fluids are indicated. Sedatives and narcotics should be avoided. Penicillin, given parenterally, is useful in combating aspiration pneumonia. Oxygen should be given. When paralysis of the diaphragm and intercostal muscles is present, a respirator may be life saving.<sup>15-17</sup> If no respirator is available other methods of artificial respiration should be tried. Unfortunately, bulbar and respiratory involvement usually co-exist. Patients with puddling of pharyngeal secretions should not be placed in a respirator unless actually unable to breathe; there is too much danger of aspiration into the tracheobronchial tree. An apparently moribund patient may show striking improvement in respiration within a few hours after removal of the tick.

#### HISTORY AND GEOGRAPHICAL DISTRIBUTION

Tick paralysis in man and animals was first mentioned in Australia more than a hundred years ago. In 1904 it was described as affecting sheep in South Africa. Later cows, horses, rabbits, guinea pigs, dogs, cats, and other animals have been found susceptible. The disease is commonest in the young of the various species; older animals appear to be relatively resistant. The first human cases in North America were reported from British Columbia in 1912, followed shortly by others from Oregon and Idaho. Since then the disease has been recognized in Crete and Yugoslavia, and many additional cases have been published from the northwestern United States and western Canada. The first cases from the eastern states were reported from South Carolina<sup>18</sup> and Georgia<sup>19</sup> in 1938.

In the northwestern United States and adjoining portion of Canada the wood tick, *Dermacentor andersoni* Stiles, is usually responsible. The distribution of cases corresponds with the northern part of the range of this tick including British Columbia, Alberta, Washington, Oregon, Idaho, Montana, Wyoming, and Colorado. No reports have yet appeared from California, Nevada, and Utah where *D. andersoni* is also prevalent, nor from North and South Dakota, Kansas, Arizona, and New Mexico which are on the fringes of its known range.<sup>20</sup> A unique case from British Columbia was attributed to the bird tick *Haemaphysalis cinnabarina*.<sup>21</sup>

In the eastern United States the dog tick, *Dermacentor variabilis* Say, has been responsible for paralysis in cases where positive identification of the tick was made.<sup>12, 14, 16, 19, 22-24</sup> Reports from South Carolina<sup>13</sup> and Washington, D. C.<sup>25</sup> of finding *D. andersoni* on patients with tick paralysis are subject to question since *D. andersoni* is not known to occur in the East. On the other hand, *D. variabilis* is widely distributed over the eastern United States as far west as Texas, Oklahoma, and Nebraska, and is also prevalent in California.<sup>20</sup>

Since 1938 three cases of tick paralysis have been reported from Georgia<sup>19, 22, 26</sup> and three from South Carolina<sup>12, 13, 18</sup> followed by single cases from North Carolina.<sup>27</sup> New York,<sup>23</sup> and the District of Columbia,<sup>25</sup> two from Kentucky,<sup>14</sup> and three from Virginia.<sup>16</sup> In all, fourteen cases occurring east

of the Mississippi River have been published, and one from Texas.<sup>24</sup> As yet the disease has not been reported from New England. Additional cases might be expected throughout the range of *D. variabilis*.

#### DISCUSSION

The Grady Memorial Hospital serves as a referral center for poliomyelitis, and all of our cases arrived with that diagnosis. McCue, Stone, and Sutton,<sup>16</sup> in a similar center at Richmond, Va., saw three patients with tick paralysis referred as poliomyelitis. This was also the initial diagnosis in many other reported tick paralysis cases. The seasonal incidence of both conditions contributes to this confusion. Tick paralysis occurs in warm weather when ticks are active, and when poliomyelitis is also likely to be prevalent. The twelve eastern cases for which date of onset is available and our four cases occurred in the following months: 1 in March, 2 in May, 6 in June, 6 in July, and 1 in August. It is especially important that those who treat acute poliomyelitis be aware of the possibility of tick paralysis since early diagnosis and tick removal may save patients who would otherwise die with a mistaken diagnosis of bulbar poliomyelitis.

Several features of tick paralysis are helpful in differentiating it from poliomyelitis. Usually there is no fever, and the spinal fluid is normal. Muscle spasm is absent, and there is little or no stiffness of the back and neck. Marked ataxia often precedes paralysis by several hours or even days, first in the legs, then in the arms. Ascending involvement is particularly suggestive of tick paralysis, while progression of paralysis without fever is uncommon in poliomyelitis. The muscular weakness in typical cases is diffuse and bilateral. It is usually but not necessarily symmetrical. Generally there is equal involvement of the legs, but sometimes<sup>22</sup>, also Case 3 the tendon reflexes return more rapidly on one side than on the other. In Case 1 the right arm was apparently paralyzed sooner and more severely than the left. In two of our patients the ankle jerks returned before the knee jerks after tick removal.

Other conditions which may be considered in differential diagnosis are polyneuritis, myelitis, infectious neuronitis (Guillain-Barré syndrome), syringomyelia, and spinal cord tumor. Such diagnoses can be dismissed when a tick is found and prompt recovery follows its removal. Furthermore these conditions usually show characteristic sensory involvement. Although hyperesthesia and paresthesia may be present in the early stages of tick paralysis,<sup>18, 28</sup>, also Cases 1 and 4 diminution or loss of skin sensation rarely if ever occurs.

Interesting clinical variations of tick paralysis may be encountered. Patients seen early may show only incoordination and absent tendon reflexes in the legs, with weakness but no complete paralysis. If the tick is removed in this stage, true flaccid paralysis may never develop (Cases 2, 3, and 4). Even with bulbar involvement the extremities may not be completely paralyzed.<sup>16</sup>, also Case 1 Especially treacherous is the tendency toward temporary improvement in the early phases.<sup>12, 15, 16, 23</sup>, also Cases 2 and 3 This may be followed abruptly by severe ascending paralysis.



The speed with which progression occurs varies widely. The patient of one reported case<sup>27</sup> showed symptoms for only two days before removal of the tick, but died of respiratory paralysis. This was the only fatal outcome in the eighteen eastern cases. In contrast, the duration of symptoms before tick removal was reported to be nine days in a case with bulbar involvement,<sup>14</sup> and ten days in another case with marked ataxia but no paralysis or bulbar signs.<sup>23</sup> Both these patients recovered.

Stanbury and Huyck<sup>2</sup> cite the greater severity of the Australian disease in which the height of paralysis may not be reached for forty-eight hours after removal of the tick, and recovery may require weeks. Local paralysis has been reported in cases<sup>29, 30</sup> where the tick was attached in the external auditory canal with homolateral facial paralysis. Also described<sup>17</sup> are ptosis of the brow and eyelid with a tick attached to the temple, and partial paralysis of the arm with a tick in the axilla. A similar case was reported from Alberta.<sup>9</sup> The factors which determine whether the paralysis is local or of the ascending type are not known.

Many fundamental questions about tick paralysis remain to be answered. The exact nature of the toxin and its mode of action have not been established. Satisfactory pathological studies on naturally occurring human or animal cases are lacking. A number of explanations have been offered to explain the apparent predilection for the young. Adults may be less likely to acquire ticks than children and more likely to remove them promptly. It is also possible that some immunity to the attachment of ticks may develop as a result of repeated exposures.<sup>31</sup> The theory that the greater size of the adult dilutes the toxin below the symptomatic level is not convincing in the light of authentic reports of cases in full-grown individuals.<sup>10, 18, 28</sup> The finding of the tick on the head or neck in the vast majority of patients is of interest. In all eighteen eastern cases the tick was attached to the scalp. Whether this is only because the tick is more likely to escape notice when hidden in the hair, or whether the toxin may more rapidly and effectively reach the central nervous system from such locations, is unknown.

The relative paucity of reported tick paralysis cases in the United States is puzzling in view of the wide distribution of *D. andersoni* and *D. variabilis*, and considering the large number of children bitten. Reporting is doubtless incomplete, although the dramatic nature of the disease invites publication. Perhaps some cases may be misdiagnosed as poliomyelitis. Surely many cases are prevented by removal of the tick before symptoms develop. Others may unknowingly be cured by tick removal when illness prompts careful examination, or possibly the tick may drop from the victim spontaneously. In the dog, recovery can occur while the tick remains attached.<sup>8</sup> It is not known whether this can happen in human patients. The incidence of tick paralysis may also be influenced by the fact, observed in animal experiments, that not all ticks of incriminated species cause paralysis, even though the host is susceptible.<sup>3</sup> It is not clear whether some engorging ticks fail to produce toxin or whether unknown factors interfere with its effect upon the host.

Thus far no cases of tick paralysis have been attributed to *Amblyomma americanum*. This tick heavily infests large areas of the southern and south-

eastern states and has recently been found, like *D. andersoni* and *D. variabilis*, to serve as a vector of spotted fever and tularemia.

## SUMMARY

1. A résumé of some known facts and unanswered questions about tick paralysis is presented.
2. Reference is made to fourteen cases previously published from the eastern United States.
3. Four new cases from Georgia are reported, from two of which *D. variabilis* was identified.
4. It is suggested that additional cases may be expected throughout the range of *D. variabilis*.
5. Tick paralysis is likely to be confused with poliomyelitis. The differential diagnosis is discussed.

The assistance of the Pediatrics staff is gratefully acknowledged. Dr. E. C. Cale and Dr. Morris Price obtained ticks from two of the patients. All tick identifications were made by Dr. Harry D. Pratt of the United States Public Health Service.

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## FAVISM

### REPORT OF A CASE IN A CHILD

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THE fava bean (*Vicia fava*) is a common food in the diet of most of the Italian families in Buffalo, N. Y. A survey of fifty Italian children entering our outpatient department revealed that this legume is eaten by 80 per cent of their families. Usually the beans are boiled and served with other vegetables. Occasionally they are eaten raw. Physically the fava bean resembles the lima bean except that it is twice its size. In this country the plant is cultivated particularly in communities with a large Italian population. In western New York State the fava bean is grown in the Eden Valley and Niagara County areas. New Jersey, Illinois, Louisiana, Florida, Mississippi, California, and the New England states also harvest large crops of fava beans. Reports from nearly all of these areas cite the seasonal incidence of favism coincident with the blossoming of the fava plant during the spring and summer.

#### CASE REPORT

C. L., an Italian male child of 4 years, was brought to the Outpatient Department of the Children's Hospital of Buffalo on July 21, 1947, with a complaint of jaundice for two days. Three days before admission, while playing in the kitchen with another child, the patient ate two raw fava beans, as did the other child. The patient was again given a small portion of cooked beans for supper. The next afternoon his mother noticed that his urine was dark orange-red colored. He voided about four times that day and the urine discoloration persisted. The boy had no complaints otherwise. The following morning his eyes appeared yellow and the abnormal urine color persisted. The child played about the house but refused his lunch. His appetite remained poor. By the next morning his jaundice had progressed to involve the skin of his body. On his way to the clinic he vomited once. His playmate did not develop any of these symptoms. The patient had no fever, chills, or convulsions. His stools were not unusual in number, consistency, or color.

Prior to this illness the patient had had several episodes of upper respiratory infections, otitis media occurring twice. The ear infections quickly responded to medication with sulfadiazine and penicillin. On one occasion following the administration of penicillin, he developed scattered eruptions over his body which the mother believed were hives. The patient's health for the previous six to seven months had been good. His birth, developmental, and feeding history were essentially negative except for an inadequate intake of vitamin D. The patient's father was born in this country, and his mother in Sicily. The parents denied the presence of asthma, eczema, hives, or other allergic manifestations in the family. The patient had one older female sibling who was in good health. Fava beans were frequently eaten raw as well as cooked by the entire family without resulting complaints. The child's paternal grandmother

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TABLE I, A. LABORATORY STUDIES

	DAYS AFTER ONSET													
	3	4	5	6	7	8	9	10	11	15	22	48	146	
Hemoglobin (Sahlb)	5.4	6.5	—	—	—	—	—	—	—	—	—	—	—	
Gm. per 100 c.c.	2.1	2.38	—	—	—	—	—	—	3.5	—	—	4.3	—	
Red blood cells (per cu. mm.) millions	3	0	—	—	—	—	—	—	0	—	—	—	—	
Nucleated red blood cells per 100 white blood cells	—	9.1	—	7,500	—	—	—	6,200	—	400	7,400	4,000	6,850	
White blood cells	16,000	8,900	—	—	—	—	—	—	—	—	1,4	—	—	
Reticulocytes (%)	—	—	—	—	—	—	—	—	—	—	—	—	—	
Differential (%)														
Bands	15	1	—	—	—	—	—	—	0	5	10	2	3	
Filaments	40	56	—	—	—	—	—	—	32	38	50	40	41	
Lymphocytes	40	35	—	—	—	—	—	68	0	47	36	54	51	
Monocytes	5	1	—	—	—	—	—	0	—	4	3	0	0	
Eosinophiles	0	0	—	—	—	—	—	0	—	6	1	4	3	
Basophiles	0	4	—	—	—	—	—	0	—	0	0	0	0	
Platelets (per cu. mm.)	319,000	—	—	—	—	—	—	—	—	—	—	—	—	
Hematocrit	22	22	—	—	—	—	—	31	—	—	—	—	—	
Icteric index (units)	100+	—	—	5-7+	—	—	—	—	—	—	—	—	—	
Serum bilirubin (mg. %)	2.96	—	—	0.23	—	—	—	—	—	—	—	—	—	
Reaction	Indirect	—	—	Indirect	—	—	—	—	—	—	—	—	—	
Sedimentation rate (mm./hr.)	44	—	—	—	—	—	—	13	—	—	—	—	—	
Urine														
Albumin	1+	0	0	0	0	0	0	0	—	0	0	—	0	
Urobilinogen $\frac{1}{20}$ dil. (qual.)	4+	3+	1+	0	0	0	0	0	—	0	0	—	0	
Stool														
Urobilinogen excretion (qual.)	4+	4+	—	—	—	—	—	1+	—	—	—	—	—	

TABLE I, B. LABORATORY STUDIES

THIRD DAY AFTER ONSET			
Blood culture		Sterile	
Blood (Kahn)		Negative	
Cephalin flocculation		Negative	
Donath Landsterner hemolysin test	12 H. 0° C.	Negative	
	12 H. 17° C.	Negative	
Cold agglutination		Negative	
Blood chloride		108 meq. %	
Blood N P N.		38 mg. %	
Blood CO <sub>2</sub> combining power		27 meq.	
Fragility			
Hemolysis—Patient	{ Begun	0 35	
and Control			
	Complete	0 12	
Bleeding time		3 minutes	
Clotting time		5 minutes	
Clot retraction		1 hour	
Tourniquet test		Negative	
Bone marrow†			
Total nucleated R B C		85,000	
Differential %			
Myelocytes (M)-----	5	Monocytes	0 5
Myelocytes (E)-----	1 5	Plasma cells	0 5
Juveniles	24 0	Disint cells	6 0
Bands	12 0	Normoblasts (B)	9 5
Filaments	9	Normoblast (P)	6 5
Eosinophils	2 5	Normoblast (O)	8 0
Lymphocytes	11 5	Megakaryocytes per 50 l p f.	20/50
Interpretation Myeloid and erythroid hyperplasia			

\*Miliequivalents

†Performed five days after onset

had had several attacks of jaundice and apparently hemoglobinuria after eating fava beans. These attacks had occurred while living in Palermo, Italy, as well as in this country. On one occasion she had become jaundiced after walking near a field of the flowering fava plant. It was also stated that her small infant daughter died shortly after eating a meal of fava beans.

Examination revealed an alert, cooperative, Italian male child of 4 years. He was moderately icteric and the mucous membranes were pale. There was neither dyspnea nor cyanosis. He had a generalized lymphadenopathy consisting of non-tender nodes 1 to 2 cm. in diameter. The heart rate was 120 per minute, and a grade II, low-pitched, blowing, apical systolic murmur was heard over the precordium. There was no cardiac enlargement and the blood pressure was 118/50. The liver and spleen could not be palpated, and there was no costovertebral tenderness. Several ecchymotic areas 2 to 3 cm. in size, presumably due to trauma, were found over the anterior aspects of both shins. The remainder of the examination was negative.

The course in the hospital was uneventful. On the second day after admission the patient's liver was found to be enlarged and extended 2.5 cm. below the costal margin but was not tender. There were no complaints. He played in his crib, ate his meals, and took an adequate amount of fluid. On the ninth hospital day he was discharged to his home to be followed in the Outpatient Department of the Children's Hospital. At the time of discharge jaundice was no longer apparent, the precordial murmur had disappeared, and the liver edge was just palpable below the costal margin. No treatment had been given other than ferrous sulfate by mouth.

The laboratory findings have been charted in Table I. On admission there was a severe anemia with stippled and nucleated red cells showing anisocytosis

and polychromatophilia, and the blood showed a reticulocytosis. The white blood count showed no significant change. The icteric index and serum bilirubin were elevated, and the urobilinogen excretion in the urine and stool was increased. Albuminuria without hemoglobinuria was also present. By the time of discharge his hematologic picture was within the normal range and has remained so over a five-month period of observation. Immunologic and other special studies were undertaken to elucidate the mechanism of the hemolytic anemia.

#### DISCUSSION

Asymptomatic jaundice occurs frequently in the first decade of life. When present in a previously healthy Italian child, erythroblastic anemia, hepatitis, leukemia, or a hemolytic anemia are considered among the most probable diagnoses. However, the diagnosis of favism can be made quickly from the history alone.

Luisada<sup>1</sup> has recently reviewed the hemolytic syndrome of favism as it occurs in Italy and this country. Approximately seven cases<sup>2</sup> have been reported in the American literature, two of which occurred in children.<sup>2</sup> The symptomatology varies from mild, painless jaundice and pallor to profound vasomotor collapse with convulsions and hemoglobinuria. Gastrointestinal complaints are believed to be more common in children. Malaise, weakness, dyspnea, and fatigue, when present, represent manifestations of the anemia. Jaundice and pallor are constant physical findings. Other signs will depend upon how soon the patient is seen after the hemolytic crisis. Hepatomegaly, splenomegaly, and cardiac murmurs may be present by the second day, particularly in children. The usual laboratory findings are those consistent with an acute hemolytic anemia. Special hematologic studies such as acid, heat, and mechanical fragility, bleeding and clot retraction time, the Donath-Landsteiner and cold agglutination tests are negative.

From the investigations of the Italian workers favism was believed to be a manifestation of sensitivity to the fava bean. Using extracts of the fava bean for skin testing, sensitivity was demonstrated in those patients subject to this hemolytic syndrome. Passive transfer experiments also corroborated this apparent reactivity to the fava bean protein. The severity of the symptoms of favism probably is not dependent upon the amount of bean ingested, for the disease can occur following inhalation of the pollen of the flowering plant, or even in suckling infants through the mother's milk. The work of Pazzi,<sup>3</sup> Lotti,<sup>4</sup> and Parlato<sup>5</sup> suggests that the antigen contained in the fava plant is a complex protein, sensitization occurring to the various fractions of the protein. During an attack skin tests and passive transfer experiments with the fava bean antigen are consistently negative. However, using other parts of the plant one may still show the patient to be sensitive to the protein fractions of the fava bean. Following recovery the patient will demonstrate positive skin tests and passive transfer antibodies to the original allergen which caused the hemolytic anemia. Pesci<sup>6</sup> believed that the hemolytic anemia was brought about by an anaphylactoid state, the bean protein acting directly upon the red cell to cause hemolysis. This

\*Since this paper was written, an additional case of favism occurring in a 5-year-old male child of Italian descent was reported. Rosen, A. P., and Scanlan, J. J. New England J. Med. 239: 367, 1948

work has never been substantiated. Similarly the toxic (an alimentary toxin by-product) and the parasitic or infectious theories held to be responsible for the hemolytic process have been discarded. The immunologic studies in the American literature have been limited to skin-testing the patient with extracts of the fava bean. In only two of the four patients on whom this test was performed was there a positive intradermal reaction. Two other patients were refed the fava bean after they had recovered from the hemolytic anemia, and both had a mild recurrence of their symptoms.

In conjunction with the observations made on our patient, an attempt was made to study the toxic properties of the fava bean upon the red cell as well as the antibody response of the patient. These experiments were carried out over a five-month period. A concentrated extract was prepared from the bean after removal from the pod. The nitrogen unit was determined by the photometric acid nitrogen method.

Intradermal injection of one cubic centimeter of the concentrated extract into a rabbit failed to demonstrate any toxicity either locally or systemically. No evidence of hemolysis or agglutination of the human red cell by the fava bean extract could be found. Serial dilutions of the fava extract and the erythrocytes were used. Both saline and plasma were used as diluents. Similarly, no precipitin antigen-antibody response could be demonstrated by using serial dilutions of the fava extract and the patient's serum.

To circumvent the possible existence of tissue anergy, skin tests and passive transfer experiments were carried out approximately five months after recovery from the disease. Varying dilutions of the extract (from 1:100 to 1:1,000,000) were injected intradermally and readings were made in 15 minutes, 24 hours, and 36 hours. Buffered saline was used as a control. Thirty-four hours after the intradermal injection of a 1:100 dilution of the extract, a 12 mm. area of induration and erythema appeared and was gone in thirty minutes. All other skin tests were interpreted as negative. Passive transfer experiments in fifteen control patients also failed to show any skin reaction.

The failure to demonstrate an antibody response in our patient is not in keeping with the findings of the Italian investigators who believed that the hemolytic anemia of favism was an allergic phenomenon. Yet the interpretation of these results is difficult, for skin tests and passive transfer experiments may be negative in other well-known allergic states. Perhaps our patient was still in a refractory or anergic phase of tissue response when these tests were done.

#### SUMMARY

This report deals with the occurrence of an acute hemolytic anemia in an Italian child following the ingestion of two raw fava beans. Jaundice and anemia were the presenting symptoms. Convalescence was rapid and uneventful. No therapy except oral ferrous sulfate was given. The patient has remained in good health over a five-month period of observation.

Studies of the toxic properties of the fava bean and antibody response of the patient over five months failed to demonstrate definite sensitization as shown by skin tests, passive transfer experiments, and precipitin reactions.



The sudden onset of asymptomatic jaundice in an Italian child should necessitate careful questioning for a recent history of fava bean ingestion.

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## HEMOPHILIA IN THE NEGRO

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### INTRODUCTION

THERE exists in the minds of many physicians considerable doubt concerning the incidence of hemophilia in the Negro. Our recent observation, therefore, of a Negro family in which two boys presented the classic findings of hemophilia led us to a review of the subject and this report of our cases is an attempt to clarify our understanding of the occurrence of the disease among Negroes.

### REVIEW OF THE LITERATURE

Standard textbooks of medicine and hematology<sup>1</sup> indicate that hemophilia occurs predominantly in Caucasians and only rarely in Negroes. More detailed review of the literature indicates that a number of cases (summarized in Table I) has been reported in Negroes, but critical evaluation of these reports throws doubts on the validity of the diagnosis in some instances. In order to evaluate these case reports properly it is well to reconsider the criteria essential to a diagnosis. Bulloch and Fildes,<sup>2</sup> in their exhaustive monograph on the subject summarized hemophilia as "an inherited tendency in males to bleed." This succinctly describes the clinical features of the disease which reflect the laboratory findings of a prolongation of the coagulation time of the blood, as first described by Wright<sup>3</sup> in 1891. Although subject to wide spontaneous fluctuation, sometimes even approaching upper limits of normal, this laboratory manifestation, once demonstrated, is practically diagnostic in the presence of a normal plasma fibrinogen level.

In addition to validity of diagnosis we were particularly interested in the racial background of those patients in whom authentic hemophilia occurred. Specifically, an attempt was made in each of these cases to determine from the data presented whether the patient was of pure Negro ancestry or of mixed racial origin.

Our studies indicate that at least eleven case reports of "hemophilia" in Negro patients has been published. The earliest report was that by Hadlock of Cincinnati in 1874.<sup>4</sup> This report indicated that the father of the patient died of hemophilic hemorrhage. Since hemophilia is not transmitted directly by the male, it is unlikely that this was an instance of true hemophilia. The bleeding in this case was most likely due to some other disturbance of hemostasis.

Koch's case<sup>5</sup> published in 1890 was of a female patient, and therefore probably was not a case of true hemophilia. For similar reasons Steiner's case<sup>6</sup> in 1900 probably should not be considered. In the same year Buck reported

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TABLE I

AUTHOR	CASE SUMMARY	COMMENT	RACIAL ORIGIN
Hadlock (1874)	History of uncontrollable bleeding from tooth socket in a 7-year-old mulatto boy. Only one such episode was reported. The father of this patient bled to death as a result of a briar scratch; an uncle, of hemorrhage from a laceration inflicted by a scythe. No laboratory substantiation of diagnosis. Genetically not compatible with hemophilia.	Diagnosis questionable	Mixed
Koch (1890)	The patient was a 6-year-old Creole, a girl whose history of bleeding was limited to a single episode of hemorrhage from the oral cavity.	Not hemophilia	
Steiner (1900)	This was a 14-year-old girl. Her pedigree revealed evidence of bleeding in both the male and female members of the family. This was reported as "the second case of hemophilia in the Negro." Sex incidence is against the diagnosis of hemophilia.	Not hemophilia	
Buek (1900)	This was an extremely brief communication concerning two patients, one of which was female. Both subjects had experienced severe nosebleeds. The ethnologic factors were not discussed.	(a) Female patient not hemophilia (b) Insufficient evidence for diagnosis of hemophilia in the male patient	
Taylor (1923)	This patient, a man, had experienced frequent episodes of bleeding as a child. Several of the male members in his family had hemorrhagic tendencies. The clotting time was consistently prolonged. Author significantly commented that the patient was "apparently tinctured with white blood."	Compatible with diagnosis of hemophilia	Mixed
Crandall (1936)	This patient, a ten-year-old boy, had bled frequently and profusely following episodes of mild trauma. The family history traced back for several generations revealed no evidence of bleeding among the male or female members. The laboratory data were quite complete and were compatible with the diagnosis. Sporadic nature of case would make plasma fibrinogen level desirable for more definitive diagnosis. Crandall described patient as being "very dark." Similarly, his parents and the siblings were heavily pigmented Negroes.	Compatible with the diagnosis of sporadic hemophilia	Pure Negro
Pachman (1937)	Pachman reported three cases, all in boys. The 15-year-old patient had a prolonged bleeding time and the author seemed inclined to consider his bleeding to have an allergic background. The other two boys, 13 and 6 years old, had histories of frequent hemorrhage in early infancy. The pedigree suggested among the male patients a transmissible tendency to excessive bleeding. The laboratory data were entirely compatible with the diagnosis.	The older child was probably not a hemophilic; the two younger boys were	One of mixed; the two one purely Negro
Birch (1937)	Three of the series of ninety-eight cases of hemophilia were Negroes of mixed racial origin.	Compatible with diagnosis of hemophilia	Mixed
Campbell (1939)	A 22-year-old man with clinical and laboratory features of hemophilia. The pedigree presented evidence of abnormal bleeding tendencies in male members of the family. Photograph of patient indicates mixed racial origin.	Compatible with diagnosis of hemophilia	Mixed

two cases,<sup>7</sup> one of which was of a female patient and therefore was eliminated by us as a true hemophilia. The information and data on the male patient were too meager to satisfy diagnostic requirements.

In 1923 Taylor<sup>8</sup> reported what was probably the first case of true hemophilia in a Negro. The genetic, clinical, and laboratory findings were presented in detail and substantiated the diagnosis. The author commented that the patient was of mixed racial ancestry.

Crandall, in 1936, presented a very significant case report.<sup>9</sup> His data satisfied all the essential diagnostic criteria. However, careful inquiry revealed no evidence of hemophilia in the patient's family. This does not preclude the diagnosis. Birch<sup>10</sup> has pointed out that a familial history is desirable but not absolutely essential to a diagnosis. These individuals with all except the genetic criteria of the disease are considered "sporadic" in contrast to the "hereditary" type. One other pertinent feature of Crandall's case is that the patient was apparently of a purely Negro origin. The description of the child's physical features as well as those of his family seemed to corroborate this. Crandall's case is, therefore, the first authentic report of hemophilia in a presumably pure Negro.

Pachman, in 1937, reported three cases of hemophilia in Negroes.<sup>11</sup> He pointed out, however, that in one case the bleeding was probably due to anaphylactoid purpura. In the other two cases the histories, symptoms, and laboratory findings were quite compatible with the diagnosis. One of these presented physical characteristics of racial intermixture whereas the history and physical characteristics of the other suggested a purely Negro racial origin with a typical hemophilic genealogy.

The most recent case published by Campbell<sup>12</sup> in 1939 had characteristics quite typical of hemophilia, but the author noted that the patient was definitely of mixed racial ancestry.

In addition to these case reports specifically concerned with hemophilia in Negro patients, other authors have mentioned the racial aspects of hemophilia in publications considering the subject generally. Birch<sup>10</sup> reported that three of her series of ninety-eight hemophiliacs were Negroes of mixed racial origin.

#### CASE REPORTS

CASE 1.—H. W., a two-year-old boy, was first admitted to the University of Illinois Hospitals in July, 1946, because of bleeding from the upper gingivae for the previous twenty-four hours. The patient was a known "bleeder" at the time of admission and had been bedridden for two weeks previously as a result of swollen joints. The past history indicated that the patient had always manifested a tendency to bleed readily. His joints swelled readily following mild trauma.

Birth history indicated that he was born by a full-term, spontaneous delivery. There was no obstetrical instrumentation; no hemorrhage was noted at birth.

The pedigree of the family is presented in Fig. 1. The patient's father was 37 years old and in good health. No information was obtainable concerning either of his parents. The patient's mother was 24 years of age and well. Her

mother died of tuberculosis. Her mother's sister had two children stated to be bleeders. One child died at the age of 5 as a result of "internal hemorrhages." The other child had seven crippling deformities due to repeated hemorrhages.

One male sibling,  $3\frac{1}{2}$  years of age, was also a known bleeder (Case 2). Two female siblings, one  $4\frac{1}{2}$  years and one 6 months of age, respectively, were living and well. No evidence of abnormal bleeding had been observed in them. A definite history of racial mixture five generations previously was obtained.

Physical examination revealed a young, cooperative, Negro boy aged 2 years, who was bleeding profusely from the frenum of the tongue. A slight mucoid nasal discharge was present. Several ecchymotic areas were present over the left forearm and elbow. The temperature was  $99.6^{\circ}$  F. rectally, the pulse 102, and the respirations 24 per minute. The skin was light brown; facial features were somewhat Caucasian.

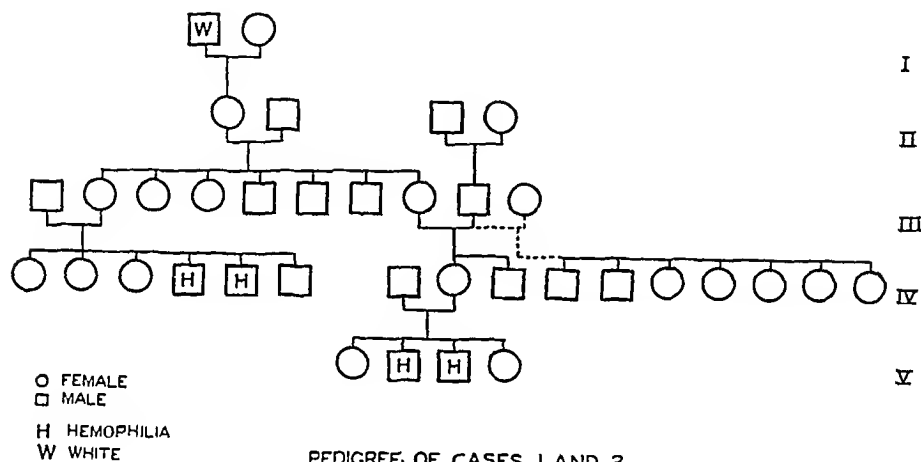


Fig. 1.

Laboratory examination revealed the following: Urinalysis was normal; red blood cell count, 4.75 million per cubic millimeter; white blood count, 14,000 per cubic millimeter; differential blood smear, 55 per cent lymphocytes, 41 per cent neutrophils, 2 per cent monocytes, 2 per cent eosinophiles. No abnormal cells were observed. Platelets were within normal limits; clotting was completed in 120 minutes (Howell's method); clot retraction was complete in six hours; the plasma fibrinogen level recorded on a later admission was 0.357 mg. per 100 e.e. of blood (normal 0.3 to 0.6 mg.).

The family history, clinical history, physical and laboratory findings, all supported the diagnosis of hemophilia.

The patient was given 250 e.e. of citrated whole blood intravenously. Twenty-four hours later all signs of bleeding had disappeared and patient was discharged in good condition.

CASE 2.—This patient, W. W., a 4-year-old Negro boy (brother of Case 1) was admitted to the University of Illinois Hospitals in June, 1947, because of painful and swollen joints for the previous twelve hours.

The history revealed that at 9 months of age the child experienced a severe hemorrhage about the left shoulder. Since that episode he was observed to bleed readily and for prolonged periods. He was a full-term infant; the delivery was spontaneous and normal. No evidence of hemorrhage was noted at birth.

Developmentally he was normal. The family history was the same as that given for Case 1 and is summarized in Fig. 1.

Physical examination revealed a thin but well-developed Negro child. He lay quietly but objected to movements of the right arm. He was cooperative, quiet, and polite. He had several ecchymotic areas 2 to 4 cm. in diameter over the left supraspinous region of the thorax. The right elbow and right knee were warm, swollen, and tender. The skin was dark brown; some Caucasian facial features were noted.

Laboratory findings were as follows: red blood count, 3.7 million per cubic millimeter; white blood count, 11,000 per cubic millimeter; differential blood smear, 57 per cent neutrophils, 4 per cent stab forms, 35 per cent lymphocytes, 4 per cent monocytes. Coagulation time, 130 minutes (Howell's method); clot retraction was complete in seven hours; bleeding time was within normal limits; urinalysis was normal.

Because of the family history, clinical history, physical and laboratory findings, a diagnosis of hemophilia was made.

The patient was given small doses of barbiturates and analgesics for his discomfort. The joint swellings subsided somewhat and he was discharged in good condition after four days of hospitalization.

*Progress Reports of Cases.*—Since their initial admissions these patients have been hospitalized repeatedly for episodes of moderate and severe hemorrhage. Most of these have followed trauma. In general, their hemorrhagic manifestations have responded well on each occasion to bed rest, small blood transfusions, and more recently to intramuscular injections of 10 mg. anti-hemophilic globulin of Fraction 1 (Cohn), which has produced prompt clinical cessation of hemorrhage plus demonstrable reduction in coagulation time for eighteen to twenty-four hours following the injection. Now at the ages of 4 and 5 years, respectively, they are robust children except for their frequent incapacities resulting from hemorrhage.

#### COMMENT

A review of the literature and this report of our cases support the impression that hemophilia does occur in American Negroes. Detailed analysis of these cases indicates that most of these individuals are of mixed racial origin on examination of their pedigrees and physical characteristics. In our two cases the pedigree presented definite evidence of Caucasian intermixture in previous generations; the patients physically evidenced this mixed racial background.

The question concerning the occurrence of hemophilia in racially pure Negro individuals cannot be entirely answered at present. Of the reported cases, that recorded by Crandall<sup>9</sup> was the first one in which the pedigree information (though limited) and anthropological features are compatible with a purely Negro racial origin. The diagnosis was well established although a plasma fibrinogen level to exclude the rare possibility of congenital afibrinogenemia would have been more conclusive. Since no known hemophilias were present in the background of this patient, it must be regarded as a case of sporadic hemophilia.

Although Bulloch and Fildes minimized the incidence of sporadic hemophilia with the statement "these 'de novo' bleeders were few in number and would be still fewer if the authors had sufficient time to investigate beneath

the surface," they did concede that such cases do occur. The British biologist Haldane,<sup>23, 24</sup> however, emphasizes the role of sporadic cases of hemophilia arising as a result of mutation of sex-linked genes as playing a very significant role in the perpetuation of this disease.

Of the cases reported by Pachman<sup>11</sup> two presented the classical features and genealogy of hemophilia. The history and physical features of one suggested a purely Negro origin. This is the only reported case satisfying all the criteria for the diagnosis of hemophilia in a presumably pure Negro. It should be noted, however, that the racial background of many Negroes is not accurately known.

For a definitive answer concerning the occurrence of hemophilia in racially pure Negroes, a study of a large population would be necessary. Because of the practical difficulties involved in undertaking such a study, authorities who had devoted much time to the study of both the West African and American Negro populations were consulted.<sup>15, 16</sup> Their studies revealed no evidence of the existence of this disease either from the folklore of the people or by actual observations of large numbers of individuals. Since they were not specifically interested in this problem at the time of their studies, these observations cannot be interpreted as conclusive. It is obvious that the comparison of large population groups of racially pure and racially mixed individuals would do much to elucidate the true racial incidence of not only hemophilia but many other diseases believed to be influenced by race. It is hoped that further observations by physicians concerning the racial incidence of hemophilia will be reported.

#### SUMMARY

The occurrence of hemophilia in the American Negro has been reviewed briefly and two cases of mixed racial origin have been reported. While hemophilia with characteristic genetic background occurs in American Negroes of mixed racial origin, the disease has been noted only once sporadically and once with characteristic genetic background in individuals of presumably pure Negro ancestry. Although hemophilia has not been noted in the West African Negro and racially pure American Negro by students of these populations, further studies of these groups would be indicated to establish this fact more definitely.

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# ACRODYNIA: A SUMMARY OF BAL THERAPY REPORTS AND A CASE REPORT OF CALOMEL DISEASE

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BILDERBACK'S classical description of acrodynia<sup>1</sup> emphasizes the fact that there has been no known etiology and therefore no specific therapy for the disease. Much interest has arisen in the new approach to the disease contained in our report in the JOURNAL OF PEDIATRICS,<sup>2</sup> based on the suggestion by Warkany and Hubbard,<sup>6</sup> of mercury as an etiologic agent and the clinical use of BAL in therapy.

Thanks to the cooperation of pediatric colleagues it has been possible to accumulate further data which seem worthy of publication at this time.

Watkins,<sup>3</sup> states that Zahorsky<sup>4</sup> was on the brink of the discovery that mercury was an etiologic agent in acrodynia but turned away from the theory when he could obtain no history of calomel intake in all his cases.

Davidson<sup>5</sup> tells me that Dr. Lesesne Smith, Sr., suggested to him between 1934 and 1938 that mercury was involved in the cause of acrodynia.

Warkany and Hubbard<sup>6</sup> finally produced the laboratory proof of the presence of mercury in the urines of acrodynia patients and they have lately published a report<sup>7</sup> of the findings in twenty cases of acrodynia. In communication with Dr. Warkany it was found that there was an overlapping of their figures with some of my reports so that in the tables I am giving their figures as fifteen instead of twenty.

Fanconi Botsztejn and Schenker<sup>8</sup> have recently published the report of a disease resembling acrodynia which they call calomel disease. It is chiefly characterized by a macular rash resembling in appearance that of red measles and caused by the ingestion of mercury in the treatment of intestinal parasites. I am adding the report of such a case to this paper.

Table I gives a summary of the cases of clinical acrodynia which have appeared in the literature or have come to my attention through personal communications.

TABLE I. URINE REPORTS IN CLINICAL ACRODYNIA

AUTHORS	WITH PROVED MERCURY	NO MERCURY FOUND	NO URINALYSIS
Warkany and Hubbard <sup>7</sup>	13	2	—
Elmore <sup>9</sup>	2	—	—
Costner <sup>10</sup>	2	—	1 (teething powders)
Smith, L. <sup>11</sup>	1	—	—
Bivings and Lewis <sup>2</sup>	1	—	—
Fox (London) <sup>12</sup>	2	—	8 (teething powders)
Ravenel <sup>13</sup>	2	—	—
Gipson <sup>14</sup>	—	—	2 (1 teething powders)
Christie <sup>15</sup>	—	1 (teething powders)	—
Watkins, Ashe and Moore <sup>3</sup>	2	—	—
Cook <sup>16</sup>	—	—	1 (teething powders)
Lewis (Eggleston Hospital) <sup>17</sup>	3	—	1 (teething powders)
Totals	28	3	13

Grand total forty-four cases of clinical acrodynia.

*Comment on Table I.*—Of thirty-one patients with clinical acrodynia on whom mercury determinations were done, twenty-eight showed mercury. Warkany<sup>5</sup> states that he and his associates observed three children whose urines showed the presence of mercury in appreciable amounts following ingestion of mercury and who showed no signs of clinical acrodynia.

There were three patients in whom mercury could not be found.

Of thirteen patients on whom no mercury determinations were done, twelve had histories of the use of teething powders. (Those commonly used contain from  $\frac{1}{10}$  to  $\frac{1}{8}$  grain of calomel.)

Table II shows the reports of the results of BAL therapy as reported in fifteen patients seen by several different observers.

TABLE II. BAL THERAPY IN CLINICAL ACRODYNIA

AUTHORS	PROMPT IMPROVEMENT OR RECOVERY	SLOW IMPROVEMENT
Bivings and Lewis <sup>2</sup>	1	—
Fox <sup>12</sup>	1	1
Elmore <sup>9</sup>	2	—
Smith <sup>11</sup>	1	—
Costner <sup>10</sup>	1	1
Gipson <sup>14</sup>	—	2
Christie <sup>15</sup>	1	—
Cook <sup>16</sup>	1	—
Watkins, Ashe, and Moore <sup>3</sup>	3	—
Totals	11	4

*Comments on Table II.*—These reports came from widely separated observers and some lacked important details necessary for accurate analysis. The disease is known to vary widely in its clinical course and most patients recover spontaneously but usually only after a prolonged illness. It was the opinion of most of the observers in this series that BAL therapy seemed to be of definite benefit.

Acrodynia does not appear with sufficient frequency in this area to permit one observer to accumulate a large series short of many years' time. Since it was possible for Fox<sup>12</sup> to find ten cases in a brief period of time it would seem to be of much greater frequency in England and it is said by Bilderback<sup>1</sup> to occur quite frequently in Australia. It is hoped that larger series will be reported where controls can be run and a single observer or group of observers can check the results of BAL therapy.

The dosage outlined in my original report was followed in this series. In view of the reports of Woody and Kotemani<sup>18</sup> it is probable that the dosage could be increased safely to at least 5 mg. per kilogram for the first day in severe cases and in extremely severe cases an even higher dose might be given with due allowances for the toxicity of the drug.\*

In this group teething powders were the source of mercury in a large majority of cases, calomel in a few, ammoniated mercury ointment in one, and mercury bichloride diaper rinse in one case. Since ammoniated mercury is commonly used on the newborn infant, sensitization easily might occur quite early in life.

\*Dr. Fox writes me that Owen of the Imperial College of Science, working with Danielli and collaborators, has made a BAL-glucoside which is much more water soluble and much less toxic than BAL. Unfortunately the chemistry is difficult, they have not been able to put the material into ampules, and, therefore, there have been no clinical trials as yet.

## SUMMARY AND CONCLUSIONS

Evidence is offered which would seem to indicate that mercury has some part in the etiology of acrodynia. If this assumption is correct it would seem that BAL therapy is logical. The cases herewith reported on whom it was used would seem to indicate it has some value.

## CALOMEL POISONING, A CASE REPORT

Baby J. B., aged 9 months, weighing 18 pounds, was brought to my office June 24, 1948, because of a rash for four days.

There were no physical findings of importance other than the rash and there was no fever. The baby was extremely restless and irritable. The rash was macular in type and covered the entire body, scalp, extremities, and the palms of the hands and the soles of the feet. The toes and the fingers were pink at the distal ends. The general appearance of the rash was that of a well-established red measles but there was no cough, no fever, no Koplik's spots, no conjunctivitis or photophobia.

The mother stated that she had used teething powders for rubbing the gums for two or three successive days one week previously and since there was some resemblance to the symptom complex of acrodynia a urine specimen was requested.

The urine specimen was examined by Warkany and Hubbard on June 27 and they reported to me several days later that mercury was present in a concentration of 50 gamma per liter.

On June 25 the rash was fading and on June 27 had faded completely. Total duration was seven days, with no therapy.

In discussing the case with Dr. Warkany he suggested it more nearly resembled calomel poisoning recently described by Fanconi and collaborators<sup>8</sup> than true acrodynia. Study of Dr. Fanconi's paper, especially the natural color photographs, confirmed this belief.

Recovery was spontaneous and the disease was of short duration.

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## PNEUMOMEDIASTINUM IN THE NEWBORN INFANT

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CYANOSIS in the neonatal period presents a difficult problem in differential diagnosis; that pneumomediastinum is one of the important possible causes is illustrated by the case recorded herewith. A few reports of this syndrome have appeared in the literature but they seem to have attracted little notice in the evaluation of neonatal mortality.

In 1940 when Gumbiner and Cutler<sup>1</sup> reviewed the literature, they could find only eight cases of pneumomediastinum in infants, of which the first two, discovered at autopsy, were reported by Guillot<sup>2</sup> in 1853. Two cases were reported by Schuler,<sup>3</sup> and one each by Kirchgessner,<sup>4</sup> H. K. Farber,<sup>5</sup> Rosenblum,<sup>6</sup> and Poeck.<sup>7</sup> Gumbiner and Cutler<sup>1</sup> stressed the importance of pneumomediastinum as a cause of death in the newborn infant as well as the diagnostic value of lateral roentgenograms of the chest. They were the first to report the therapeutic use of needle aspiration. Since 1940 twelve additional cases have been reported (see Table I), including three by Lowman and Culotta,<sup>12</sup> of which one showed the classical clinical syndrome of circulatory and respiratory embarrassment with precordial bulge. (This infant died before needle aspiration could be attempted.)

### CASE REPORT

K. D., a one-day-old male infant, was extremely cyanotic, comatose, and scarcely breathing when admitted to Abington Memorial Hospital. Delivery had been spontaneous without instruments at another hospital. Respiration was slower than usual in becoming established but resuscitation had not been necessary, and nothing abnormal had been noted by the attending physician on examination of the infant after delivery. Twelve hours later cyanosis was first observed. The cyanosis deepened progressively and the infant was referred to the Abington Hospital twenty-four hours after birth.

On arrival he was comatose and appeared moribund. The skin was "purplish-black" in color, with numerous petechiae scattered over the thorax and abdomen. The anterior fontanel was not bulging. Slight, symmetrical respiratory excursions and an early precordial bulge were noted. Fine, diffuse râles were heard over the right lung. These were more marked at the base. Breath sounds over the left lung were moderately diminished. The heart could not be outlined by percussion. Heart sounds were best heard in the midsternal region but even there were almost inaudible. No murmurs were heard.

Oxygen by mask was administered immediately, and caffeine sodium benzoate, 60 mg., was given intramuscularly. Within one hour the rate and depth of respiration had improved, and a decrease in cyanosis was noted. Oxygen therapy was continued, and during the following twelve hours the cyanosis diminished and the infant's general condition improved. The respiratory rate, however, still approximated 80 per minute. There was noted at this



Fig. 1.

Fig. 1.—Anteroposterior view, thirty-six hours after birth and prior to needle aspiration. Atelectasis of the right upper lobe. (Bedside x-ray taken while child was in critical condition.)



Fig. 2.

Fig. 2.—Anteroposterior view sixty-four hours after birth sixteen hours after 17 c.c. of air were aspirated. Atelectasis is no longer present.

Fig. 3.—Seven days after birth. Normal chest film prior to discharge from hospital.

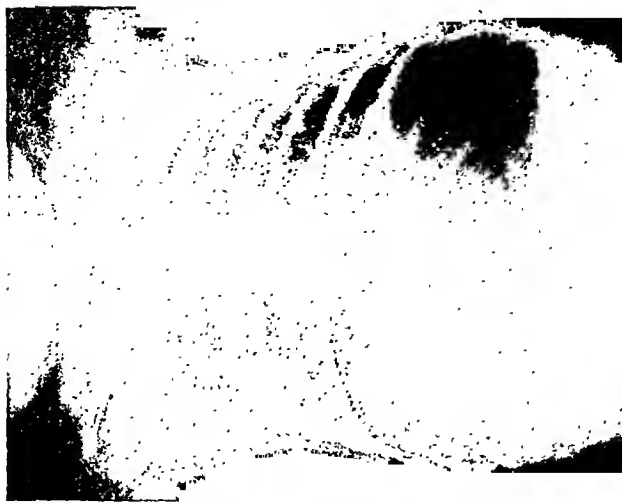


Fig. 3.

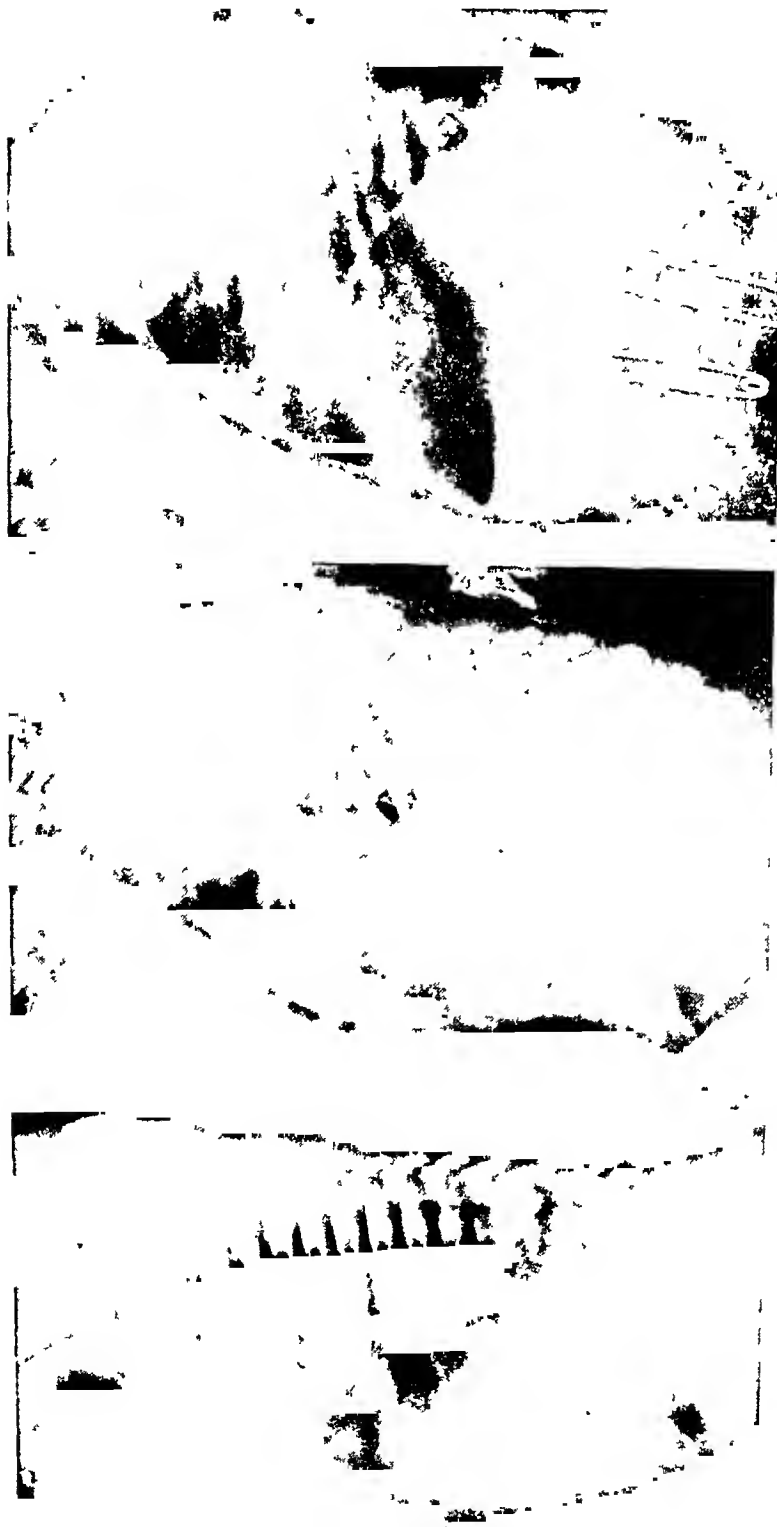


Fig. 4.

Fig. 4.—Lateral view, thirty-six hours after birth and prior to needle aspiration. Air is seen in the anterior mediastinal space. The heart is displaced posteriorly.

Fig. 5.—Lateral view, sixty-four hours after birth, and sixteen hours after 17 c.c. air were aspirated. Less air is seen in the anterior mediastinal space, than in Fig. 4.

Fig. 6.—Lateral view, seven days after birth. Normal chest film preceding discharge from the hospital.

Fig. 5.

Fig. 6.

TABLE I

AUTHOR	CASE	YEAR	AGE OF PATIENT	CYANOSIS	DYSPNEA	ATELEC-TASIS	M.L. AIR OBTAINED*	RESULT
Gumbiner and Cutler <sup>1</sup>	Case 1 Case 2 Case 3 Case 4	1940	30 hr.	Extreme Slight Slight Moderate	Severe Slight Slight Moderate	Patchy	6	Rec. Rec. Rec. Rec.
De Costa <sup>2†</sup>		1940	12 hr.†	Present	Severe			Death
Fisher <sup>3</sup>		1941	12 hr.†	Extreme	Moderate	L. Lung R.U.L.	No	Rec.
Biering <sup>4</sup>	Case 1	1941	12 hr.†	Moderate	Severe		Yes§	Rec.
Smith and Bowser <sup>11</sup>	Case 2	1942	12 hr.†	Extreme	Severe	R. Lung	No	Death
Lowman and Culotta <sup>12</sup>	Case 1 Case 2 Case 3	1945	12 hr.† 12 hr.† 12 hr.†	Extreme Slight Moderate	Severe Slight Moderate		No No No	Rec. Rec. Rec.
Heald and Wilder	Case 1	1948	12 hr.	Extreme	Severe	R.u.L.	17	Rec.

\*By therapeutic needle aspiration of mediastinum (parasternal).

†A. Second case mentioned, but not described. Aspiration, 6 c.c. air, site not specified.

‡First symptoms noted about twelve hours following birth.

§Air, under pressure, aspirated, but amount not specified.

||Pulmonary interstitial emphysema found at autopsy.

time a marked precardial bulge with the physical findings of emphysema over the entire thoracic cage.

A roentgenogram of the chest showed collapse of the right upper lobe, and widening of the mediastinum bilaterally. The lateral view showed air confined to the anterior mediastinal space, with posterior displacement of the heart.

About forty-eight hours after birth the infant's condition became critical. The respiratory rate was 88 and the sternal region bulged anteriorly in a striking manner. A 20-gauge needle was inserted into the third interspace just to the right of the sternum and 5 c.c. of air were aspirated without difficulty. Following this procedure there was definite but slight improvement. A second aspiration performed three hours later yielded 12 c.c. of air, and this was followed by great improvement during the next twelve hours.

Because of the marked degree of hyperventilation that was present during the critical stages of the illness, blood chemical determinations were obtained. Bicarbonate was 10.5 meq. per liter and the chlorides 107.5 meq. per liter. This acidosis was corrected by the administration of 150 c.c. of 1/6 molar sodium lactate by hypodermoclysis.

During the twenty-four hours following needle aspiration the temperature ranged between 99.6 and 103° F. Ten thousand units of penicillin were given intramuscularly every three hours. On the third day of treatment the temperature was normal and remained so until discharge from the hospital. The precardial bulge subsided within thirty-six hours following the needle aspirations. The respiratory rate fell gradually so that on the tenth hospital day it was 30 per minute.

#### COMMENT

In 1939 Macklin<sup>13</sup> first described the results of his studies on the pathogenesis of pneumomediastinum in experimental animals. He stated that the pathologic process begins whenever the anatomy of the lung is so altered that a localized or generalized emphysema is the end result. Such emphysema gives rise to overdistention of the alveoli with air finding its way into the pulmonary vascular sheaths. The actual inlets for the air into the sheath system are multiple, minute ruptures in the alveolar bases which overlie the finer ramifications of the pulmonary blood vessels. The air then dissects down the sheaths to the hilum of the lung and from there into the mediastinum. In none of his experimental animals was Macklin able to demonstrate torn or ruptured alveoli grossly. This process, as described above, is known as pulmonic interstitial emphysema.

Further extension of this process, with the air invading the mediastinum, gives rise to pneumomediastinum. The pressure in the mediastinum may become so great that either death ensues or decompression occurs by extension of the process in one of three directions: (1) down into the retroperitoneal space and even further into the groin and leg; (2) upward into the axilla, the wall of the chest, the root of the neck, and the face; (3) forward between the parietal pleura and the pericardium to appear as large blebs overlying the heart.

It is the third type of extension which gives rise to the distressing symptoms described in the case reported. The negative pressure in the anterior mediastinum becomes positive with resultant pressure on the large veins to the heart. This results in diminished venous return and circulatory embarrassment. The pressure in the anterior mediastinum can be relieved in one of two



ways: (a) by needle aspiration and (b) by rupture of the mediastinal wall into the pleural space with resultant pneumothorax. Experimentally, Macklin<sup>13</sup> has shown that the mediastinal wall, strained past endurance, ruptures into the pleural space, causing pneumothorax. This relieves mediastinal pressure, thus improving the circulation; and, at the same time, by collapsing the lung and eliminating the area of alveolar distention, it prevents further leakage.

According to the above reasoning, the development of spontaneous pneumothorax should be regarded as a fortunate mechanism whereby pneumomediastinum is relieved. Our case and the others represent a syndrome which results from a failure of this mechanism to operate in the face of a marked mediastinal emphysema. Although these severe cases are relatively rare, it is probable that pneumomediastinum as a precursor of pneumothorax has about the same incidence as the latter, which, in the newborn infant, is said to be 1 per cent.<sup>14</sup>

#### SUMMARY

Pneumomediastinum in a newborn infant can produce an alarming and unusual clinical picture characterized by: (1) extreme cyanosis; (2) marked precordial bulge; (3) almost absent heart sounds; (4) rapid shallow respirations.

Anteroposterior and lateral films of the chest in the case described showed atelectasis of the right upper lobe and air in the anterior mediastinum. The lateral film is pathognomonic of this syndrome. Relief of symptoms (essentially cardiac) was obtained by needle aspiration of the anterior mediastinum, from which 17 c.c. of air was obtained. Recovery was uneventful.

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## THE OCCURRENCE OF A TYPE FIVE SULFADIAZINE-RESISTANT HEMOLYTIC STREPTOCOCCUS

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### INTRODUCTION

THE circumstances and conditions which led to the development of sulfonamide-resistant hemolytic streptococci have been reviewed recently.<sup>1</sup> Available information suggests that conditions of continuous mass sulfadiazine prophylaxis as they existed in the Armed Forces during World War II<sup>2, 3</sup> were conducive to dissemination, and possibly to the development of strains of hemolytic streptococci resistant to the action of sulfadiazine.

The spread of sulfonamide-resistant hemolytic streptococci to the civilian population has received little attention. The first reported instance of civilian infections due to these resistant organisms occurred in 1946 when Johnson and Hartman<sup>4</sup> described a small epidemic due to a sulfadiazine-resistant group A, type 19 hemolytic streptococcus, in Cooperstown, N. Y. Another survey made in Boston<sup>1</sup> revealed one infection due to a group A, type 19 sulfadiazine-resistant hemolytic streptococcus out of 167 infections studied. In both instances it was concluded that the resistant organisms encountered in these civilian populations were of the same type as occurred in the Armed Forces and had probably been introduced by Army or Navy personnel. The possibility of sulfonamide-resistant strains of hemolytic streptococci developing in the general population has received little investigation, and no reports of such an occurrence have appeared in the literature to date.

Because sulfadiazine-resistant, group A, hemolytic streptococci had been encountered in Cooperstown in 1946,<sup>4</sup> it was decided to test the sulfonamide sensitivity of hemolytic streptococci in this community eighteen months later to determine if these resistant type 19 organisms had persisted and were still a cause of infections. It is the purpose of the present communication to report the results of this survey in which a moderately sulfadiazine-resistant group A, type 5 hemolytic streptococcus was encountered, and also to comment on some of the factors pertinent to its occurrence.

### MATERIALS AND METHODS

The sources of hemolytic streptococci were cultures from both adults and children from Cooperstown and surrounding areas who were seen in the outpatient department or wards of the Mary Imogene Bassett Hospital from January to May, 1948. These patients had clinical evidence of a streptococcal infection or were admitted to the hospital for observation or study and were

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found to harbor hemolytic streptococci. Most of the strains of hemolytic streptococci were obtained from the nasopharynx of patients who had pharyngitis, but others were isolated from infected wounds, abscesses, draining ears, vaginal discharges, and blood cultures. No attempt was made to do a widespread survey on a healthy group to determine carrier rates.

Culture swabs were streaked on the surface of 5 per cent rabbit blood agar plates which were incubated for twenty-four hours at 37° C. Single colonies of beta-hemolytic streptococci were transferred to broth on the following day and following incubation were checked for purity by restreaking on blood agar.

All hemolytic streptococci isolated were grouped and typed by the capillary precipitin technique<sup>5</sup> with the available diagnostic sera. Due to the difficulty of obtaining typing sera for all types, sera only for those types some strains of which were known to be sulfonamide-resistant were used, i.e., types 1, 3, 6, 17, and 19. Upon encountering type 5 resistant strains, all cultures were typed using this serum also. The sulfonamide sensitivity was determined by the method of Wilson,<sup>6</sup> using horse serum and sodium sulfadiazine; known resistant and sensitive strains were always run as controls.

#### RESULTS

Ninety-six strains of group A hemolytic streptococci isolated from patients in Cooperstown and its environs were tested for sensitivity to the action of sulfadiazine. The type distribution determined by the use of the six available diagnostic sera and sulfonamide sensitivity are listed in Table I.

TABLE I. TYPE\* DISTRIBUTION AND SULFADIAZINE RESISTANCE OF GROUP A HEMOLYTIC STREPTOCOCCI

INFECTING TYPE	NO. CASES	NO. SULFADIAZINE-RESISTANT STRAINS
1	8	0
3	0	0
5	6	2†
6	1	0
17	0	0
19	0	0
NC‡	51	0
Total	96	2

\*Only six sera (types 1, 3, 5, 6, 17, and 19) were available for typing by the precipitin method.

†These two type 5 strains were resistant to 5 mg. per cent sodium sulfadiazine.

‡NC indicates strains not classified by the precipitin method with available diagnostic sera.

Six type 5 hemolytic streptococci were encountered in this study, of which two strains showed evidence of moderate resistance to the action of sulfadiazine, i.e., grew in 5 mg. per cent sodium sulfadiazine. These type 5 strains were isolated from children 11 years of age or younger (see Table II). All of the other strains were completely susceptible in vitro to sulfonamide action. No type 19 sulfonamide-resistant strains, which had been present in this locality previously,<sup>4</sup> were isolated.

Since this is the first report of the isolation of sulfadiazine-resistant group A, type 5 hemolytic streptococci in the general population, further analysis of

TABLE II. CLINICAL DATA OF TYPE FIVE INFECTIONS

PATIENT	AGE	DIAGNOSIS	DATE OF CULTURE	TREATMENT PRIOR TO CULTURE	SULFADIAZINE RESISTANCE	REMARKS
M51	11	Tonsillitis and pharyngitis	3/ 5/48	Received a combination of sulfadiazine and sulfathiazole 6 days prior to culture.	1 mg.	Two weeks later patient developed nephritis and active rheumatic heart disease.
M66	5	Acute tonsillitis	3/17/48	None prior to culture.	1 mg.	Responded to treatment with sulfadiazine.
M82	8	Pharyngitis	3/29/48	None prior to culture.	1 mg.	Responded to treatment with sulfadiazine and sulfathiazole.
M86	8	Pharyngitis	3/30/48	None prior to culture.	1 mg.	None.
M94	9	Pharyngitis	4/ 3/48	None prior to culture.	5 mg.	Responded to treatment with sulfadiazine.
M95	10	Pharyngitis	4/ 5/48	None prior to culture.	5 mg.	Responded to treatment with sulfadiazine.

the clinical data pertinent to this occurrence has been attempted (see Table II). The first patient (M54) from whom a type 5 strain was isolated had received a combination of sulfadiazine and sulfathiazole for six days prior to the time of his culture; the organism isolated from his throat grew in 1 mg. per cent sodium sulfadiazine; two weeks later this patient developed nephritis and active rheumatic heart disease. The next three type 5 isolations also grew in one milligram per cent sodium sulfadiazine; none of these patients had a history of sulfonamide treatment prior to culture. Of these patients two were treated with sulfadiazine or a combination of sulfadiazine and sulfathiazole and recovered promptly from their infections without complications; one received no treatment.

The patients (M94 and M95) who were infected with the type 5 hemolytic streptococci resistant to 5 mg. per cent sodium sulfadiazine were diagnosed as having a pharyngitis, were treated with therapeutic doses of sulfadiazine and made an uneventful recovery. These patients had not been given any sulfonamide medication prior to the time that they were cultured.

The patients with type 5 infections lived in different localities in the community and gave no history of any contact or association with one another. The two resistant type 5 organisms and also the nonresistant type 5 strains were sensitive to 0.015 units of penicillin as determined by the method of Rammelkamp.<sup>7</sup>

During this period of study the type 5 infections differed in no way clinically from those due to other types of hemolytic streptococci nor did they present any therapeutic or epidemiologic problem. The number of hemolytic streptococcal infections in this community during this period of study was considered to be average when compared with a similar period for other years. Sulfonamides are prescribed quite extensively in this area in usual therapeutic dosages for treatment of common infections, but chemoprophylaxis is employed rarely if at all.

#### DISCUSSION

The present report was initiated by a desire to determine whether sulfonamide-resistant type 19 hemolytic streptococci, which had been the causative organisms of a small epidemic in Cooperstown, N. Y., in 1946,<sup>4</sup> were still causing infections in this community after a lapse of eighteen months. The results of this study indicate that no type 19 organisms were encountered in ninety-six sporadic infections in 1948. Similarly, type 3 hemolytic streptococci, which were responsible for a large number of infections during the 1946 study,<sup>4</sup> were not encountered. Although mass carrier surveys of the general population were not carried out, the present data suggest that the population of this community was immune to type 19 and type 3 infections and that organisms of these types, if present, did not cause infections.

The isolation of two type 5 sulfonamide-resistant hemolytic streptococcus strains was unexpected. Neither the type 5 resistant strains nor the four non-resistant type 5 strains encountered were in any way unusual as far as the

type of infection they produced. Apparently the infections produced by these streptococci responded to sulfonamide therapy and in only one instance did any serious complications occur (see Table II).

The degree of *in vitro* sulfonamide resistance shown by the type 5 strains is not high, but is regarded as significantly elevated. By the Wilson method<sup>6</sup> sulfonamide-susceptible streptococci grow in the presence of zero and one milligram per cent sodium sulfadiazine but are inhibited by higher concentrations. Strains which are sulfonamide-resistant grow in the presence of 5, 25, or 125 mg. per cent of the drug. Epidemics due to type 3 hemolytic streptococci resistant to 5 mg. per cent sodium sulfadiazine were encountered during World War II.<sup>8, 9</sup> Few strains belonging to type 3 achieved resistance greater than this degree. The failure of chemoprophylaxis to offset epidemics due to these sulfonamide-resistant type 3 strains<sup>8</sup> suggests that resistance to 5 mg. per cent sodium sulfadiazine is of epidemiologic significance and may be of clinical significance.

The most common sulfonamide-resistant strains of group A hemolytic streptococci encountered in the Armed Forces during World War II were types 1, 3, 6, 17, and 19.<sup>1, 2, 10</sup> These type strains had degrees of sulfonamide resistance ranging from 5 to 125 mg. per cent sodium sulfadiazine. Although there are no reports of the occurrence of type 5 sulfonamide-resistant hemolytic streptococcal infections in the literature, type 5 organisms capable of growing in 1 mg. and 5 mg. per cent sodium sulfadiazine were encountered sporadically in the Navy,<sup>9</sup> but apparently did not present any epidemiologic or clinical problems.

As concerns the origin of the type 5 sulfonamide-resistant hemolytic streptococci encountered in this study, the most likely explanation is that they were the same as those encountered in the Navy during the mass chemoprophylaxis programs. The possibility that they could have arisen in the general population cannot be ruled out, but is not likely. Information referable to the possibility of sulfonamide-resistant hemolytic streptococci occurring in the general population is as follows: (a) all strains of hemolytic streptococci preserved prior to the advent of sulfonamide therapy which were tested for sulfonamide resistance were found to be sensitive to the action of sulfadiazine<sup>1, 9</sup>; (b) except for the type 19 sulfadiazine-resistant hemolytic streptococci, all other types encountered in the earlier study from Cooperstown<sup>4</sup> were sensitive to the action of sulfadiazine; (c) of more than 350 strains of hemolytic streptococci from Boston tested for sensitivity to sulfadiazine, only one resistant strain was isolated.<sup>1, 11</sup> All other surveys of the incidence of hemolytic streptococci having properties of increased resistance have been conducted in the Armed Forces and are not contributory to this problem in the general population. Although the civilian studies have not been extensive, they indicate that the occurrence of even moderately resistant strains of hemolytic streptococci has not been commonly encountered in strains isolated at random from civilian populations in two localities.

Whether or not hemolytic streptococci can develop resistance to sulfonamides in the civilian population during commonly prescribed dosages of sulfonamides is not definitely known. However, present data would seem to indicate that the treatment of patients with therapeutic doses of sulfonamides did not tend to cause the development of resistant strains of hemolytic streptococci.<sup>12</sup> Similarly, small groups of carriers of hemolytic streptococci did not develop resistant organism during varied regimens of chemoprophylaxis.<sup>13, 14</sup>

Experimental evidence concerning the mechanisms involved in the development of sulfonamide-resistant strains of hemolytic streptococci have not been reported to date. Preliminary observations<sup>15</sup> indicate that certain features of the sulfonamide resistance developed by hemolytic streptococci are similar to those of the resistance to penicillin by staphylococci and streptococci.<sup>16, 17</sup> Strains of hemolytic streptococci made resistant to sulfonamides by transfer in media containing increasing amounts of a sulfonamide develop resistance to the drug, only to lose this resistance when transferred in drug-free media. On the contrary, sulfonamide-resistant hemolytic streptococci recovered from human infections in the field have maintained their resistance after over 100 passages through media containing no drug. These observations would seem to indicate that *in vitro* resistance is of a temporary nature while *in vivo* resistance is permanent.

At present there is a paucity of information concerning the possibility of hemolytic streptococci acquiring resistance to sulfonamides, penicillin, or other antibiotic agents in the general population. Only when these organisms present epidemiologic or therapeutic problems do they receive any attention. The fact that a previously unreported sulfonamide-resistant type 5 hemolytic streptococcus has been observed in a civilian community indicates that the incidence of sulfonamide-resistant hemolytic streptococci in the general population, derived from the Armed Forces, may be greater than is generally realized. It is also of some interest that the two type 5 sulfonamide-resistant infections mentioned in this report occurred in children, since only one previous publication<sup>4</sup> has reported the isolation of sulfonamide-resistant hemolytic streptococci from children.

The possibility that hemolytic streptococci might develop resistance to sulfonamides in a civilian population could be determined only by extensive sampling under circumstances similar to those of this study. It is hoped that future surveys and fundamental investigation may elucidate the mechanisms concerned in this problem of sulfonamide-resistant hemolytic streptococci.

#### SUMMARY

The results of testing ninety-six strains of group A hemolytic streptococci for sensitivity to the action of sulfadiazine are reported. Two strains of type 5 hemolytic streptococci which were resistant to 5 mg. per cent sodium sulfadiazine are reported. The circumstances of the appearance of these resistant strains, in a civilian community, are discussed.

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## THE ETIOLOGY OF ERYTHEMA NODOSUM

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WHILE erythema nodosum has long been recognized as a clinical entity most of the prevailing ideas concerning its etiology have developed within the past thirty years. At various times specific causative organisms have been advanced as the etiologic factor. Rosenau<sup>1</sup> isolated a polymorphous diplobacillus which he thought was the causative agent, but there has been no confirmatory evidence of it nor has any other organism been shown to be consistently associated with the disease.

For many years following the work of Mackenzie<sup>2</sup> a majority of workers have felt that erythema nodosum is closely related to the rheumatic syndrome. Another group headed by Wallgren<sup>3</sup> and other Scandinavian workers has felt that tuberculosis plays an overwhelmingly important role in the etiology.

In more recent years erythema nodosum has been reported associated with coccidioidomycosis,<sup>4</sup> lymphopathia venereum,<sup>5</sup> sulfone administration,<sup>6</sup> and with streptococcal infections of the upper respiratory tract.<sup>7</sup> Perry<sup>8</sup> has recently presented an excellent review of the subject.

The incidence of erythema nodosum in this country is low in comparison to the reported incidence in the Scandinavian countries. During the five-year period of 1941 to 1946, I found the records of only six cases of erythema nodosum in the files of the Children's Hospital of Philadelphia\* and of the St. Christopher's Hospital for Children. These cases, with one observed in private practice, supply the clinical material for the present report.

CASE 1.—E. W., a Negro boy, aged 7 years, was admitted to Children's Hospital of Philadelphia, May 29, 1942, with fever, swollen cervical nodes, and a swollen left testicle. He developed erythema nodosum two days after admission. Old tuberculin 0.001 mg. was strongly positive. A roentgenogram of the chest showed a density spreading out from the right hilum into the pulmonary parenchyma. The appearance was considered compatible with a diagnosis of pulmonary tuberculosis. Gastric washings were negative for tubercle bacilli. The erythema nodosum subsided in a period of ten to twelve days.

CASE 2.—M. W., a Negro girl, aged 8 years, was admitted to Children's Hospital of Philadelphia, May 28, 1943, with fever and tender swellings on the anterior surface of the lower legs of two weeks' duration. A diagnosis of erythema nodosum was made. Old tuberculin 0.001 mg. was strongly positive. Chest x-ray disclosed some enlargement of the cardiac silhouette. There was marked prominence of the left hilar shadow believed to be enlarged lymph nodes. Faint mottling was noted in the left infraclavicular region suggestive of tuberculous infiltration. The erythema nodosum subsided four days after admission.

\*From the Pediatric Department of Temple University Philadelphia.

<sup>8</sup>Records kindly furnished by courtesy of Joseph Stokes, Jr., M.D., Children's Hospital of Philadelphia.

These two patients illustrate the association of erythema nodosum with tuberculous infection. Wallgren<sup>3</sup> has shown that the great majority of children with erythema nodosum in Scandinavia have positive tuberculin reactions and that chest x-ray often shows evidence of tuberculous infiltration. Wallgren feels that the nodules develop at the time that tuberculo-protein sensitivity appears. He was able to demonstrate this fact with repeated tuberculin tests on a group of student nurses who had their first exposure to tuberculous infection while under his close observation. The erythema nodosum developed in these nurses coincidentally with the appearance of a positive tuberculin test.

As a result of Wallgren's work there has been a tendency to ascribe a tuberculous etiology to nearly all cases of erythema nodosum where patients have a positive tuberculin reaction. It seems likely that in some of these cases the positive tuberculin reaction is an incidental finding and that the erythema nodosum is due to a different etiologic agent. Löfgren<sup>5</sup> states that most workers in this field agree that unless the tuberculous lesion shows some evidence of activity, another cause for the erythema nodosum must be sought.

CASE 3.—L. S., a Negro boy, aged 8 years, was admitted to Children's Hospital of Philadelphia, Jan. 19, 1945, with a diagnosis of erythema nodosum. The throat and tonsils were noted to be moderately inflamed on admission. Old tuberculin 0.001 mg. was moderately positive.

This patient had been followed in the chest clinic since 1938 because of a positive tuberculin reaction. Serial roentgenograms of the chest had shown hilum densities considered to be compatible with tuberculosis.

The lesions cleared in eight days. Gastric washings were negative for tubercle bacilli. The chest x-rays showed no change during the illness with erythema nodosum.

It seems likely that the upper respiratory infection precipitated the erythema nodosum in this case and that the positive old tuberculin test was merely incidental. The fact that the chest x-ray remained unchanged is significant. Collis<sup>7</sup> has shown that some patients with erythema nodosum and negative tuberculin tests have marked skin sensitivity to streptococcal nucleoprotein. His findings have been confirmed by Coburn and Moore<sup>9</sup> who reported the production of exacerbations after the injection of the nucleoprotein of the hemolytic streptococcus intra-antaneously. They found high antistreptolysin titers in twenty of twenty-two cases of erythema nodosum.

In spite of the fact that erythema nodosum has often been attributed to rheumatic infection, it is difficult to find cases in which rheumatic carditis was initiated by an attack of erythema nodosum. Wallgren<sup>3b</sup> described a patient who developed arthritis and carditis seven days after the onset of lesions. The carditis was confirmed by electrocardiographic changes. Mackenzie<sup>2</sup> reported twenty cases of erythema nodosum in patients with cardiac lesions. However, only five of his patients developed endocarditis during the attack. Rheumatic infection may be the etiologic agent in the following case report.

CASE 4.—M. F., a white girl, aged 8 years, was admitted to St. Christopher's Hospital, May 22, 1942, with a history of easy fatigability and pains in both thighs of two months' duration. There had been two spontaneous nosebleeds in the previous two months, and occasional abdominal pains. Reddish, painful lumps appeared over the anterior surfaces of both tibias three or four days be-

fore admission. Physical examination revealed no cardiac enlargement or murmur. There was no evidence of respiratory infection. The erythrocyte sedimentation rate was rapid. Old tuberculin 0.10 mg. was strongly positive. Chest x-ray revealed calcification within the hilum showing a healed first infection type of lesion. The lung parenchyma was clear. There was no cardiac enlargement. Electrocardiograms revealed a P-R interval of 0.16 second. The amplitude of the QRS complexes was low. Interpretation was myocardial depression.

It is difficult in this patient to decide whether the erythema nodosum initiated a mild carditis or whether it was just an incident in the course of a mild rheumatic infection. It seems unlikely that tuberculosis was a factor in this patient since the chest x-ray revealed a healed and calcified lesion at the hilum which remained unchanged during the erythema nodosum.

Sulfonamide administration, especially the use of sulfathiazole, has been associated with the development of erythema nodosum.<sup>6</sup> Clinically and histologically the skin lesions show no differences from those associated with other disease processes. However, the distinguishing factor is the rapid disappearance of the nodules when the drug is stopped. The following cases were associated with the administration of a sulfonamide:

CASE 5.—R. W., a white boy, aged 6 years, was admitted to Children's Hospital of Philadelphia, April 23, 1944, with fever, malaise, and a purulent left otitis media. Sulfathiazole was administered 0.5 Gm. every four hours and after five days the temperature was normal and the child seemed improved. However, on the fifth hospital day an eruption typical of erythema nodosum appeared on the anterior surfaces of both tibias. Old tuberculin 0.01 mg. was negative. The sulfonamide medication was discontinued as soon as the nodules were noted, and in two days the lesions had cleared except for some discoloration of the skin.

CASE 6.—T. W., a white girl, aged 6 years, was admitted to Children's Hospital of Philadelphia, Nov. 14, 1943. History revealed that the patient had been ill three weeks before admission with an acute upper respiratory infection and otitis media which subsided with sulfadiazine medication. The complaint at the time of admission was fever and frequency of urination. Urinalysis revealed many pus cells with clumps in each high-power field.

The patient was given sulfathiazole 0.5 Gm. every four hours. The urine cleared promptly but on the third hospital day nodules typical of erythema nodosum appeared on the lower legs and a few on the forearms. Sulfathiazole medication was discontinued and the nodules completely cleared in five to six days.

Whether the erythema nodosum in these cases was actually due to the sulfathiazole administered or was due primarily to the infection for which the sulfonamide was given is a problem which lends itself to considerable speculation. Löfgren<sup>10</sup> thinks that the sulfonamide acts merely as an activator and that the infection is the primary factor in the development of erythema nodosum. The rapid disappearance of the nodules when the sulfonamide is discontinued argues in favor of sulfonamide sensitization being the primary factor.

The development of the nodules after the injection of Frei antigen in a case of lymphopathia venereum has been reported,<sup>5</sup> and similarly erythema nodosum has followed the application of a tuberculin test in a patient with

extreme tuberculin sensitivity.<sup>5</sup> It is unusual for it to result from diphtheria toxoid immunization, but the following case illustrates that it may be a possibility.

CASE 7.—W. M. a white boy aged 6 years, was seen in private practice Sept. 11, 1943, for a routine checkup and found to be in excellent condition. He had been immunized against diphtheria during infancy with alum-precipitated diphtheria toxoid injections. A booster injection of 0.5 c.c. alum-precipitated diphtheria toxoid was administered into the left upper arm at the end of the checkup examination.

Two days later the child was seen at home with a high fever, a red, tender, swollen, left upper arm, and nodules typical of erythema nodosum present over the anterior surfaces of both lower legs. The nodules followed the usual course, gradually fading during the next seven or eight days. Old tuberculin 0.01 mg. was negative and there was no evidence of an intercurrent infection of the upper respiratory tract.

In reviewing the literature, I found one other case of erythema nodosum which was apparently precipitated by the administration of diphtheria toxoid. Löfgren's<sup>10</sup> patient had a primary tuberculous infection of the right great toe with secondary enlarged nodes in the right groin. Following the administration of diphtheria toxoid, typical lesions of erythema nodosum appeared on the anterior surfaces of the lower legs. Löfgren felt that in his case the tuberculosis was the primary factor and the diphtheria toxoid merely the activator. In my patient, on the other hand, the injection of diphtheria toxoid in a previously immunized boy appears to be the primary factor in the development of the erythema nodosum.

#### COMMENT

The small group of cases presented illustrates the wide variety of etiologic factors associated with the clinical syndrome identified as erythema nodosum. The factor which is common to all the cases presented may be considered to be a nonspecific sensitization. This sensitization may be to tuberculo-protein, to the nucleoprotein of the hemolytic streptococcus, to coccidioidin, to the sulfonamide molecule, or to diphtheria toxoid. In addition should be mentioned the possible sensitization to the Frei antigen and perhaps to other antigenic substances.

It seems logical to conclude that erythema nodosum is not a specific disease but is more likely a reaction in a sensitized individual to a variety of sensitizing agents.

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## BLOOD SUGAR IN NEWBORN INFANTS

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ALTHOUGH investigations of the blood sugar of newborn infants have been made, knowledge is still fragmentary concerning the accepted range of values during this period of life and concerning the influence of the method of determination on the values.

The purposes of the present investigation were: (1) to determine the change in mean blood sugar level of infants during the growth period from birth to the sixth day; (2) to determine the variability of the blood sugar level among normal infants and to ascertain whether this variability changes during the growth period; (3) to ascertain the variability which measured the error of the method, and (4) to compare blood sugar determinations as made by the micromethod and the macromethod.

### REVIEW OF LITERATURE

The results reported in previous studies on blood sugar determinations in normal infants vary widely (Table I). This may be due to the variety of methods, the source of the blood samples, and the length of the fasting periods, as well as to the age of the infants. As indicated in Table I, the greatest reported range is from 0 to 0.32 Gm. per 100 c.c.; the minimal average value is 0.060 and the maximal average value is 0.126 Gm. per 100 c.c.

During the first week of life the blood sugar readings have been shown to be lower than at a later period. Miller and Ross<sup>28</sup> found low blood sugar values within the first forty-eight hours of life in infants who presented no abnormal findings. In McKittrick's<sup>25</sup> study of seventy-three normal infants, the mean blood sugar determination was 0.078 Gm. per 100 c.c. for the first week and 0.086 Gm. for the second week. These determinations were made on samples of blood taken three and one-half hours postprandially by the Folin method. Köhler<sup>21</sup> expressed a belief that variations in the blood sugar readings, as determined by Bang's method three to four hours after feeding, were closely associated with changes in weight of the infant. There was a decrease in the blood sugar readings until the third day; then a rise occurred. This fall was more rapid than the change in weight but the rise in blood sugar readings generally occurred two days before the weight increased. There appeared to be a leveling off of the rise between the seventh and the thirteenth days.

Götzky's<sup>2</sup> determinations of the blood sugar by Bang's method showed a rapid increase from the first day until the end of the first week, after which a gradual decrease took place until the twelfth day. Greenwald and Pennell<sup>19</sup>

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used the Folin micromethod to determine the blood sugar in samples of blood drawn three hours after the last feeding. The determinations were made on ninety-four infants whose ages varied between 1 and 10 days. These readings showed a slow but definite rise during this period.

Brown<sup>13</sup> found that the blood sugar values varied with age. On twelve infants less than 2 weeks of age, the blood sugar readings as determined by MacLean's method ranged from 0.072 to 0.097 Gm. per 100 c.c.; the average being 0.087 Gm. The infants older than 6 weeks had a blood sugar range of 0.086 to 0.116 Gm. per 100 c.c. and a mean of 0.106 Gm. Martinolli<sup>17</sup> found a significant rise in the blood sugar of 0.022 Gm. per 100 c.c. from the first to the seventh day of life, as did Bentivoglio.<sup>16</sup>

Others besides Köhler found a decrease in the values for blood sugar during the first three or four days of life. Ferri and Giudilli<sup>23</sup> showed that blood sugar determinations made on samples of blood drawn from twenty newborn infants four hours after feeding decreased until the third day. This decrease was 0.008 Gm. per 100 c.c. from the mean value on the first day to the mean on the third and fourth days. Schretter and Nevinny<sup>18</sup> found that the minimal blood sugar reading was made on the third day, after which the averages increased until the twelfth day. The determinations of capillary blood sugar on ten infants who were followed by Buonocore<sup>21</sup> showed a decrease from the mean of 0.0801 Gm. per 100 c.c. within the first eight hours after birth to the mean of 0.0727 Gm. on the second day, and then a gradual increase occurred to 0.0911 Gm. on the tenth day of life. However, Ketteringham and Austin<sup>24</sup> found a decrease from the average of 0.103 Gm. per 100 c.c. at birth to 0.067 Gm. in three to six hours; then a steady rise occurred in the average blood sugar readings to 0.076 Gm. on the third day. Sherman and his associates<sup>14</sup> found a slight decrease in the carbohydrate content of the blood between the first and the third day but after that time there was no apparent change. Hartman and Jaudon<sup>22</sup> found a very marked tendency for the blood sugar to fall into the hypoglycemic zone during the first day of life and these subnormal values persisted for several days.

Joslin and his associates<sup>33</sup> stated, without citing any evidence, that stabilization of the blood sugar level occurs during the first twenty-four hours of life. Reenkola,<sup>26</sup> using the Hagedorn-Jensen method, determined the blood sugar on samples of blood drawn from 100 newborn infants. The variability as determined by the standard deviation was 0.0170 Gm. per 100 c.c. one-half hour after birth, and then it decreased to 0.0109, 0.0146, and 0.0145 Gm. on the second, fifth, and eighth days, respectively. Since the variability decreased within the first two days of life, he interpreted this decrease as a sign of stabilization of the blood sugar level during this period. Schretter and Nevinny<sup>18</sup> showed that the difference between the maximal and minimal blood sugar readings decreased during the first week. This they interpreted as a sign of stabilization during the first week.

Buonocore<sup>21</sup> is the only one who made determinations of sugar on both the capillary and venous blood of infants. The values for the venous blood sugar were either equal to, or ranged to 23 mg. per 100 c.c. lower than, the values for capillary blood sugar.



Schretter and Nevinnyis <sup>18</sup>	1930	1 to 12	38	2.5 to 3.75	Hagedorn-Jensen	0.033-0.146	0.076
Greenwald and Pennell <sup>19</sup>	1930	1 to 10	94	3	Folin	0.060-0.100	0.083
Svenssgaard <sup>20</sup>	1931	4 to 14	11	5 to 5.5	Hagedorn-Jensen	0.066-0.099	0.060
Köhler <sup>21</sup>	1932	1 to 13	40	3.5 to 4.5	Bang	0.034-0.092 (1st day)	
						0.02 (later)	
Holman and Mathieu <sup>22</sup>	1933	1	51	—	Schaffer	0.050-0.170 (cord)	0.090
Ferri and Giordillo <sup>23</sup>	1935	First 5 or 7	20	4	Bang	0.055-0.173	0.085
Ketringham and Austin <sup>24</sup>	1938	3 hr. to 3	37	—	Folin-Malmros	0.046-0.110	0.072
McKittrick <sup>25</sup>	1940	1 to 14	73	3.5	Folin	0.010-0.160 (1st week)	0.078
						0.053-0.118 (2nd week)	0.086
Reunkola <sup>26</sup>	1940	0.5 hr. to 8	100	3	Hagedorn-Jensen	0.036-0.120	0.073
Pinnagalli <sup>27</sup>	1940	6 to 21	12	4	Hagedorn-Jensen	0.081	0.081
Miller and Ross <sup>28</sup>	1940	First 48	17	—	Folin-Malmros	0.066-0.094	0.099
Zondek and Wolfshutz <sup>29</sup>	1941	First 6	23	3	Hagedorn-Jensen	0.060	0.080
						0.0-0.32	
Hanley and Horn <sup>30</sup>	1943	1 to 6 hr.	129	—	Folin-Wu	0.052-0.095 (Macromethod)	0.066
						0.035-0.14 (Micro-method)	0.077
						0.47-0.120 (Capillary)	0.084
Buonocore <sup>31</sup>	1946	1 hr. to 10	10	4	Hagedorn-Jensen	0.047-0.116 (Venous)	0.076



## PROCEDURE

Samples for determination of blood sugar were taken from each of fifty-one normal newborn babies daily for the first six days of life. Blood for the sugar determinations by a modification of Somogyi's micromethod<sup>34</sup> was obtained from a skin puncture in the heel of the infant. Two samples of blood were taken, each with a separate pipette, for each set of duplicate determinations. The first sample of blood was taken within the first twelve hours after birth. The subsequent samples were made at least four hours after the last feeding either in the morning before the 6 A.M. feeding or in the evening before the 6 P.M. feeding. One of the objectives of the study was to compare morning with evening readings, and another was to study the possible change of blood sugar with age in this period. It was, therefore, necessary not only that one-half of the readings for the six days of life of the infant be made in the morning and the other one-half in the evening, but also that the days of age on which these were made should be equally represented among the six days of life studied. The studies were, therefore, stratified in such a way that for some infants the observations alternated morning and evening; some of the observations were made in the order two morning, two evening, one morning, one evening; or some in the order two morning, one evening, two evening and so forth for all possible combinations.

The following procedure was used: To 4.1 c.c. of distilled water was added 0.1 c.c. of blood rinsed into this water. To this was added 0.4 c.c. of  $\text{Ba}(\text{OH})_2$  and the mixture was allowed to stand at least five minutes. Then 0.4 c.c. of  $\text{ZnSO}_4$  were added. A finger cot was placed over the top of the tube containing the above mixture. The mixture was placed in the refrigerator and allowed to stand three to sixteen hours before the procedure was finished. In order to complete the determinations, the tubes were centrifuged three minutes. For the blank, 2 c.c. of distilled water and 2 c.c. of Somogyi's reagent were mixed. These tubes were heated ten minutes in a boiling water bath. When they were removed from the bath, 1 c.c. of Nelson's reagent<sup>35</sup> was added to each. The tubes were shaken immediately and allowed to cool to room temperature. The contents of each were made up to a volume of 25 c.c. with distilled water and mixed. The unknown was read against the blank in the spectrophotometer.

In order to compare the blood sugar determinations made by this micro-method with the determinations made by the macromethod of Folin and Wu,<sup>36</sup> 5 c.c. of venous blood were drawn from the internal jugular vein of some of the infants shortly after blood had been taken from the skin puncture in the infant's heel for determinations by the micromethod. No readings obtained by the Folin-Wu method were used if the blood contained any clots.

## VARIABILITY

*Variability of the Method.*—Examination was made of the duplicate observations to estimate the size of the technical error. The data provided 306 sets of such paired readings (fifty-one infants times six days) which could be used for this purpose. The average value of the difference between the duplicates was 4.8 mg. per 100 c.c. Measured as standard deviation the technical error

was 4.4 mg. per 100 c.c.;\* this represents 7.2 per cent of the mean value for the blood sugar; Fig. 1 shows graphically the variation represented by the technical error of the method.

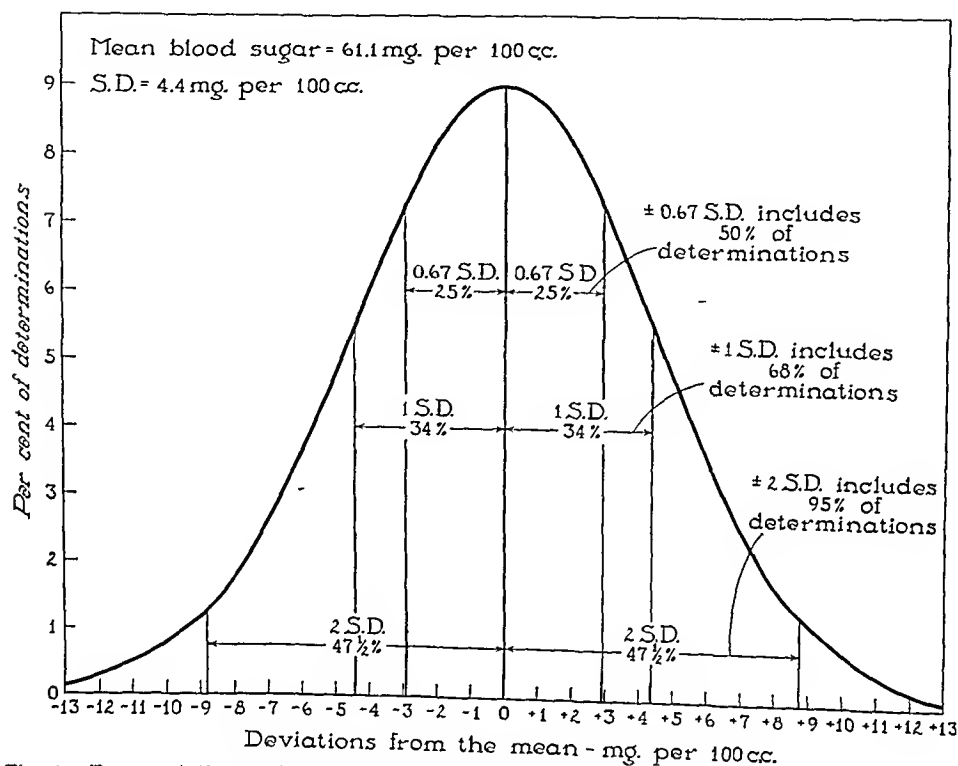


Fig. 1.—Representation of the variability of repeated determinations on the same individual, based on 306 sets of duplicate determinations.

*Macromethod and Micromethod Compared.*—In order to confirm the differences between the blood sugar determinations made by the micromethod with the determinations made by the macromethod of Folin and Wu, fifty-four samples of venous blood were drawn from thirty-six infants shortly after blood had been taken from the skin puncture of the heel for determination of sugar by the micromethod. The mean value for the blood sugar determined by the Folin-Wu method was  $66.8 \pm 1.8$  mg. per 100 c.c. and by the micromethod it was  $59.4 \pm 1.3$  mg. The distribution of these fifty-four paired differences between the macromethod and the micromethod determinations is shown in Fig. 2. The mean differences were  $7.4 \pm 1.3$  mg. per 100 c.c. and the standard deviation was 9.6 mg. The mean differences amount to about 12 per cent of the blood sugar values and are statistically significant. One should observe in Fig. 2 that although the differences indicate a large value for the Folin-Wu method, due to the intrinsic variability of the methods, the macromethod will appear to give a

\*Each pair yields an estimate of the variance based on one degree of freedom, equal to one-half the squared difference of the two observations. The average of these is an estimate of the variance of the technical error, based on 306 degrees of freedom.

smaller value in about 20 per cent of the determinations when these two methods are compared. The fact that the variability for both methods, as measured by the standard deviation, was the same, affords confidence in the comparative precision of the micromethod.

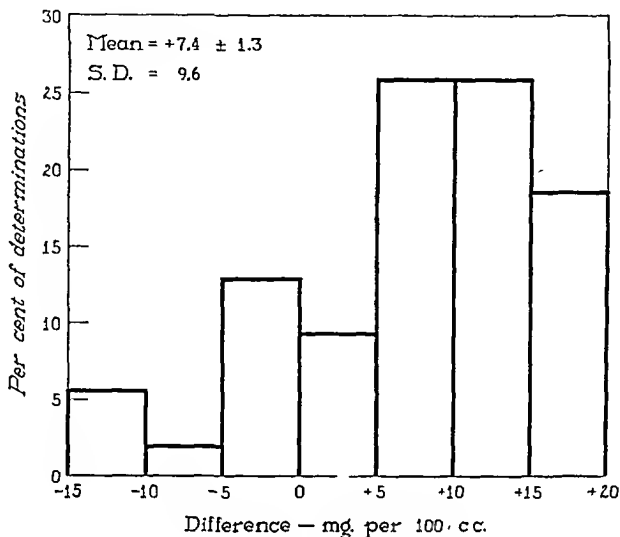


Fig. 2.—Distribution of differences between determinations by the macromethod of Folin-Wu and the micromethod.

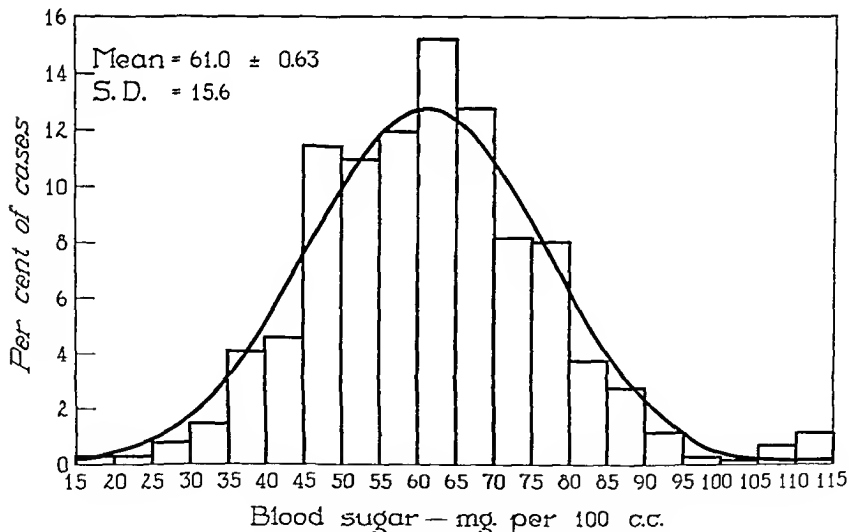


Fig. 3.—Distribution of 612 blood sugar determinations (micromethod) for fifty-one normal infants; comparison with the gaussian curve.

*Variability Among Infants.*—For the entire group of 612 determinations (fifty-one infants times six days times two duplicates) made for the fifty-one infants, the mean value was  $61.0 \pm 0.63$  mg. per 100 c.c. and the standard deviation

tion was 15.6 mg. The corrected intraindividual variability\* for these babies was 13.8 mg. per 100 c.e. (22.6 per cent of the mean) and the interindividual variability† was 7.0 mg. per 100 c.e. (11.5 per cent of the mean). The range of these readings was from 15.0 to 120.0 mg.; the low values were unaccompanied by any signs or symptoms of hypoglycemia. The distribution of these readings is compared with the gaussian or normal curve in Fig. 3. The observations appear to be satisfactorily represented by the normal curve.‡

*Comparison of Morning and Afternoon Values.*—A comparison of the blood sugar determinations was made between samples of blood drawn in the morning and those drawn in the evening (Table II). It was seen that the values for the sugar in the morning appear, on the average, to be somewhat higher than those in the evening (2.5 mg. per 100 c.e. or about 4 per cent of the mean). The difference is small and not quite statistically significant in the light of its error ( $P = 0.06$ ) but it is possible that a larger sample would render it so. Such difference as exists is probably related to the length of the interval between the last feeding and the withdrawal of the blood, the morning readings having been taken, on the average, about four hours after the last feeding, the evening readings about five hours after the last feeding.

TABLE II. COMPARISON OF BLOOD SUGAR READINGS MORNING AND EVENING

OBSERVATION	NO.	BLOOD SUGAR (MG. PER 100 C.C.)	
		MEAN*	STANDARD DEVIATION
Morning reading	306	62.25 $\pm$ 0.91	16.0
Evening reading	306	59.76 $\pm$ 0.97	17.0
Difference	—	2.49 $\pm$ 1.34	—

\*The number after the  $\pm$  is the standard error of the mean.

*Relation to Age.*—When the blood sugar is examined in relation to the age of the baby (Table III, Fig. 4) it is seen that there is a distinct rise during the first six days of life. A line fitted to the data by least squares yielded the equation  $S = 51.3 + 2.8A$  where  $S$  is the blood sugar in milligrams per 100 c.e. and  $A$  is the age in days. There is thus indicated an average daily increase of 2.8 mg. per 100 c.e. during the first six days of life. The observations showed a decrease from the first to the second day and from the fifth to the sixth day but these decreases are not statistically significant and probably represent random

TABLE III. COMPARISON OF THE DAILY BLOOD SUGAR READINGS

DAY OF LIFE	NUMBER*	BLOOD SUGAR (MG. PER 100 C.C.)	
		MEAN†	STANDARD DEVIATION
1	102	56.7 $\pm$ 1.6	16.4
2	102	54.8 $\pm$ 1.4	14.4
3	102	57.1 $\pm$ 1.2	12.0
4	102	62.1 $\pm$ 1.5	15.6
5	102	68.3 $\pm$ 1.7	17.0
6	102	67.1 $\pm$ 1.2	12.5

\*There were two determinations at each observation and the number of individuals for each day was fifty-one.

†The number after the  $\pm$  is the standard error of the mean.

\*Variability of repeated determinations on the same infant.

†Variability between mean values for different infants.

‡Neither the "skewness" ( $0.02 \pm 0.07$ ) nor the kurtosis ( $0.21 \pm 0.20$ ), measuring departures from the gaussian curve, was statistically significant.

fluctuations rather than biologic changes. As has been noted previously, opinion has been expressed in the literature that the blood sugar values stabilize during the early days of life. As judged by the intradaily variability, measured as the standard deviation, there is no clear evidence that such stabilization occurs during this period. The average intradaily variability was 14.7 mg. per 100 c.e. or 24.1 per cent of the mean. During the first three days of life there was some indication of a lowering of the variability (16.4 to 12.0 mg. per 100 c.e.).

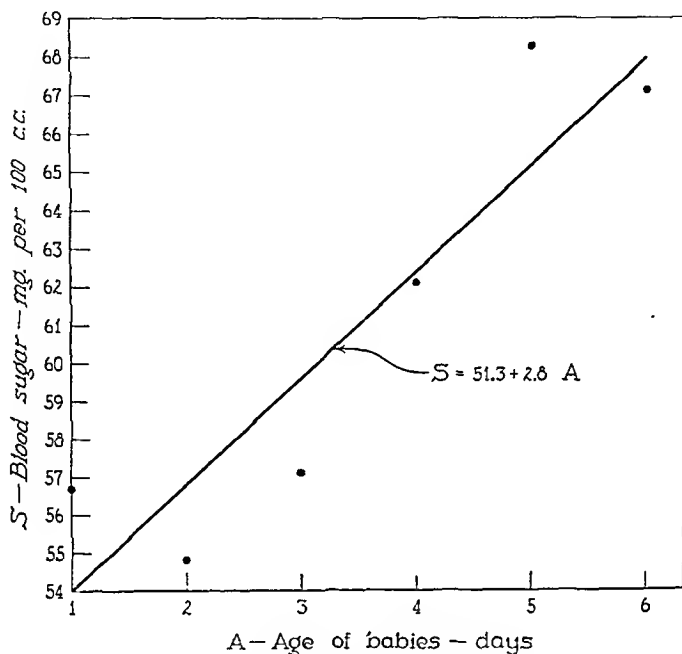


Fig. 4.—Mean value for blood sugar (micromethod) in relation to age. The regression line was determined by the least square method.

#### SUMMARY

Blood sugar readings on fifty-one normal newborn infants were made on duplicate samples of blood by means of a modification of Somogyi's method during the first six days of life. The technical error, measured as the standard deviation, estimated from the 306 differences between the duplicates, was 4.4 mg. per 100 c.e. (7.2 per cent of the mean). The average value for blood sugar as determined by the Folin-Wu method was significantly higher than the mean value for blood sugar as determined by the micromethod. For the entire group of 612 determinations the mean was  $61.0 \pm 0.63$  mg. per 100 c.e. and the standard deviation was 15.6 mg. The corrected intraindividual variability for these babies was 13.8 mg. per 100 c.e. (22.6 per cent of the mean) and the interindividual variability was from 7.0 mg. per 100 c.e. (11.5 per cent of the mean). The range of the determinations was 15.0 to 120.0 mg. per 100 c.e. When the low values were obtained no signs of hypoglycemia were observed. The blood sugar determinations made on samples of blood drawn in the morning were higher than

those made on blood drawn in the evening, but not by an amount that is statistically significant, although perhaps a larger sample would have rendered it so. When the blood sugar was examined in relation to age, an average increase of 2.8 mg. per 100 c.c. per day during the first six days of life was found. There was no evidence of stabilization of the blood sugar during this period.

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# POST-TRAUMATIC AMNESIC CONFABULATORY SYNDROME IN A CHILD

## A CASE REPORT AND DISCUSSION

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ALTHOUGH there is an abundant literature of post-traumatic psychotic reactions of the Korsakoff type in adults, few cases are on record of the occurrence of such a syndrome in children. Blau<sup>1</sup> stresses the point that none of the children described in his twenty-two case reports showed hallucinatory or confabulatory tendencies "which are so common in the acute traumatic psychoses of adults." Studies by Meyer,<sup>2</sup> Berger,<sup>3</sup> and Kasanin<sup>4</sup> did not include the occurrence of the syndrome in a child. A more recent report by Schilder<sup>5</sup> makes mention of the psychological significance of the post-traumatic behavior as expressed in hallucinations and dreams in which the patient sometimes "relives the traumatic experience." However, such occurrence was said to be limited to minor head injuries.

The following case report is noteworthy because it not only describes a rather typical amnesic confabulatory syndrome in a child but also illustrates a close relationship of the patient's post-traumatic behavior with pretraumatic emotional turmoil and conflict.

N. F., a 10-year-old schoolgirl, was brought to a Maryland hospital in an unconscious condition about one-half hour after she had been struck by an automobile after alighting from a bus. When admitted to the accident room she was in deep coma; however, there was no evidence of external injuries except for a small hematoma over the right frontal area and a tiny laceration in the left malar region. There was no bleeding from the ears and both tympanic membranes were intact. No escape of spinal fluid was evident from any orifice. The pupil of her left eye was somewhat larger than that of the right but both reacted promptly to light and the eye movements were unrestricted. No stiffness of the neck was present; however, abdominal reflexes as well as all tendon reflexes of both extremities could not be elicited. The Babinski was positive on the left side.

Blood pressure, temperature, pulse, and respirations were within normal limits and remained constant upon repeated examinations.

Though still profoundly comatose, the child became quite restless eight hours after admission. At that time her pupils were equal and there was no positive Babinski. All other reflexes were unchanged.

The child's comatose state continued for about twenty-eight hours, when she began to show responses to painful stimuli and at the end of forty-eight hours she executed certain direct commands, such as, "Stick out your tongue," "Open your eyes," etc.

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Laboratory findings one day after admission showed a red blood cell count of 4,500,000 with a color index of .85; the white blood cell count was 15,550 with seventy-nine per cent neutrophile, 17 per cent lymphocytes, 1 per cent monocytes, and 3 per cent myelocytes.

The examination of the urine showed no abnormality except for clumps of white blood cells.

Röntgen examinations of the skull and cervical spine were negative for fracture or dislocation. On the third hospital day, the patient responded to direct questions but seemed sleepy and stuporous. Abdominal reflexes were equal and active but tendon reflexes were still absent.

A spinal fluid examination showed normal pressure, 35 mg. per cent protein, normal sugar, and 27 lymphocytes.

On the fourth day drowsiness was still pronounced but the child began to repeat questions in an echolalie fashion. Examination of the eye grounds revealed 0.5 dioptric elevation of the left disc and a small area of detachment of the chorioretina in the same eye.

On the fifth day the patient suddenly sat up and seemed to be perfectly clear mentally. However, she knew nothing of her whereabouts or about the accident but recognized members of her family and recalled events of the past. The neurological signs began to improve and on the eighth day the edema around the left disc showed regression. Except for absent reflexes in the left lower extremity, there were no abnormal neurological findings.

On the eleventh day, for the first time since regaining consciousness, the child became restless. Her right pupil was now larger than the left and no reflexes could be elicited in the right lower extremity at this time. Her restlessness and hyperactivity continued for the next four days but her general condition seemed to improve when, in the late evening of the fifteenth hospital day she suddenly awakened from her sleep and fearfully told of seeing "snakes, bugs, and beetles of various colors" in her bed. She was completely disoriented and appeared extremely frightened. In spite of heavy sedation, she tried to climb out of bed and this behavior continued unabated, except for brief periods during which she was more lucid and could recall some events of the past and present; however, she showed a tendency toward filling memory gaps by making up a story in a confabulatory fashion. The child's confusional state grew increasingly more severe and careful neurological evaluations showed a constantly changing picture without definite evidence of a localized lesion.

Two additional lumbar punctures on the twenty-first and twenty-third hospital days, respectively, revealed clear fluid of normal pressure and a cell count of 2. A diagnosis of hematoma, subdural or epidural, was made and the patient transferred to the Johns Hopkins Hospital for surgical treatment.

Examination on admission showed the previously described hyperactivity, restlessness, and disorientation. There was a large hemotoma in the middle of the forehead but otherwise physical and neurological findings were normal. A spinal fluid examination was negative except for a cell count of 25. An electroencephalogram twenty-eight days after injury showed an irregular wave pattern with varied slow frequency of two-per-second waves to seven-per-second



waves. The occipital areas were out of phase with constant two- to three-per-second waves in the right occipital area and somewhat slower frequencies in the parietal and temporal regions. The slowing became more marked on hyperventilation (Fig. 1).

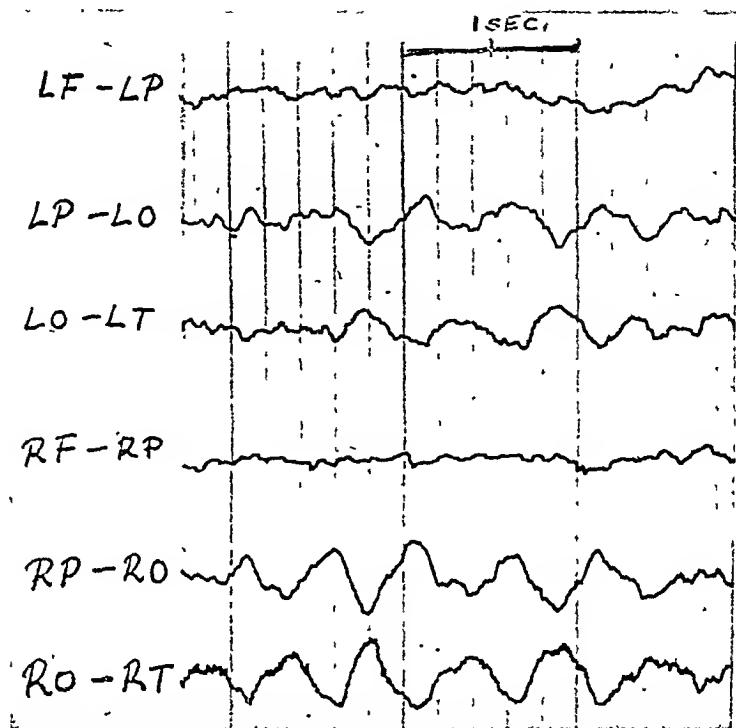


Fig. 1.—Electroencephalogram on twenty-eighth day. Bipolar tracing. (From the Electroencephalographic Laboratory, Henry Phipps Psychiatric Clinic, Dr. Leonard J. Gallant.)

On the basis of these findings, the neurosurgical consultant saw no immediate need for surgical intervention. Because of the persistence of the child's psychotic behavior and the increasing difficulties in management, a psychiatric consultation was requested. When the psychiatrist saw the girl, she was sitting in a chair staring at the floor. There was a marked flatness of facial expression and a striking absence of appropriate response to the people present. She answered questions rapidly but automatically and recalled past events without much difficulty. Without hesitation she told of being in a hotel at present, that it was in Baltimore and that she had dropped in because she just "happened to pass by." When asked where she ate her meals, the patient promptly replied, "I just go to places and eat. I guess this place is as good as any to stay in." Retention of digits was limited to four forward and there was a striking deficit in recall of immediate events. At times she showed perseveration of words with a tendency to become indignant when the examiner repeated an unanswered question. At such times the tendency to confabulate became more pronounced. The patient showed no recollection of the accident or the events that led up to it.

Information obtained from the child's father revealed that she had always been a very active, tomboyish child who enjoyed athletics a good deal but had few feminine interests. She liked to kick a football with her two older brothers, whereas she had little in common with her two-year older sister who is "the perfect young lady," according to the informant.

In her relations with other people she was somewhat shy but stubborn and independent. Her vivid imagination made her "dress up" many a story she told, which frequently annoyed her parents. She enjoyed listening to mystery stories on the radio and was an avid reader of "Dick Tracy."

Her birth and early development were normal. She progressed poorly in school during the first two years but subsequently improved her record.

Because of her interest in athletics, she had a tendency to associate with older boys and when she returned home one afternoon after having played with her friends she asked her mother what "fuck" meant. After the latter recovered from the initial shock, she inquired into the reason for her question and learned that the girl had been taking part in sex play with some of the boys, which caused her mother to be even more shocked. The mother then forbade the girl to leave the house until she had confessed to the priest; however, two days later, when the girl begged to be permitted to go swimming, her mother consented. It was during that swimming excursion that the accident occurred.

The father described himself as a rather worrisome and excitable person who is overly concerned about his children's health. His wife, on the other hand is calm and cool headed and an excellent manager of the home. There are no undue difficulties between the various family members, according to the father.

N's behavior in the hospital continued to fluctuate between periods of marked excitement with hallucinations of a visual and tactile nature, disorientation, and confabulation interrupted by relatively lucid periods during which she showed a marked memory deficit concerning recent events; however, the content of her hallucinations was of a rather constant pattern. She felt something "crawling in her pants," she saw blood in her pants, she looked for "these things" in her pants and dress, felt something "jabbing against her leg," adding that only a doctor could "jab something into her." The excitement became particularly marked during doctors' visits when she pulled her clothes off to "look for these things." She addressed one of them as "Dr. Virgin" and was quite flirtatious with him. She seemed particularly fearful of entering the bathroom and did so only after considerable persuasion. Another fear was to walk on grass and of bugs under the bed sheets. During episodes of severe excitement she yelled, "Don't beat me. I have to tell someone. I have to talk to someone."

This behavior pattern continued until the thirty-fifth day, when she calmed down considerably and only occasionally showed hallucinations. However, there was still a marked memory deficit as regards recent events. She began to join in the group activities, was "show-offish" when talking with the doctors

and quite flirtatious with them. An electroencephalogram still showed abnormalities as described previously but was considerably improved (Fig. 2). She was discharged from the hospital on the forty-fifth day. Except for mild memory impairment, she had completely recovered.

The treatment while in The Johns Hopkins Hospital was primarily of psychiatric nature and consisted of about a dozen visits by the psychiatrist. As little emphasis was placed on formal testing as was consistent with an evaluation of her condition and the child was encouraged to express her fears in the treatment situation without obtaining verbal reassurance as such. The major source of emotional support for the patient was her private nurse who, under the guidance of the psychiatrist, provided the child with the personal attention so essential in her fearful state. Outside stimulation was reduced to a minimum, as were visits by her parents. As the patient grew calmer, she began to participate in games with other children with increasing self-confidence.

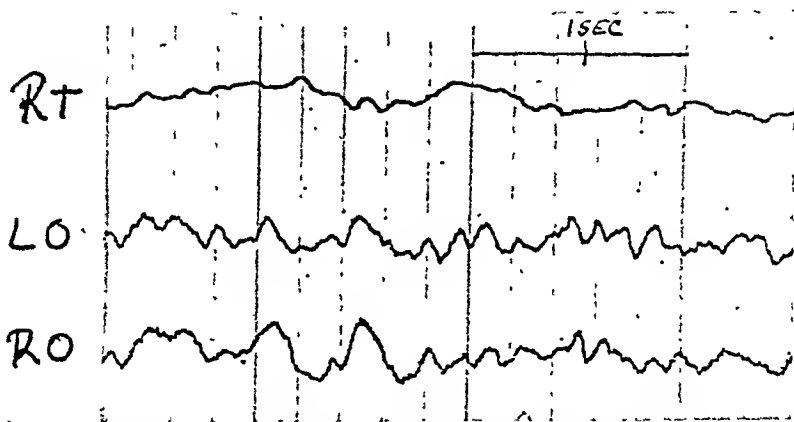


Fig. 2.—Electroencephalogram of thirty-fifth day. Monopolar tracing. (From the Electroencephalographic Laboratory, Henry Phipps Psychiatric Clinic. Dr. Leonard J. Gallant.)

In her relationship with the psychiatrist she displayed a playful somewhat uneasy assertiveness at first which was in contrast with her attitude toward various diagnostic procedures, during which she was quite serious and obediently cooperative. No attempt was made to encourage the child to verbalize emotional conflicts as it was not feasible, for geographical reasons, to continue treatment following discharge from the hospital. In addition, it was believed that her marked deficit state would not have been conducive to efforts of that type.

A follow-up visit one month after discharge revealed that the patient's memory had returned to normal even though she continued to be amnesic of the accident and events leading up to it. Her behavior had changed in so far as she had been less impulsive; however, she seemed considerably more "spoiled" and was thinking "that she could get away with everything at home as she could in the hospital," according to her parents. She remembered the three

principal physicians who took care of her and described the visiting pediatrician as the "one who liked the girls," the resident pediatrician as the "one who was handsome" and the psychiatrist as "that real smart one." During her visit she was somewhat uneasy and "show-offish," treated the doctor as a "pal," and at times playfully ignored his questions and suggestions. She complained of having been too much confined to the home and that her mother would no longer let her play with the boys "because of my sickness." She made no reference to the accident, however.

#### DISCUSSION AND SUMMARY

The preceding case report illustrates the occurrence of an amnesic-confabulatory syndrome in a ten-year-old child on the fifteenth day following a severe head trauma after an initial five-day period of coma and semicoma and a ten-day interval of gradual but definite improvement. The manifestations of the patient's delirious reaction showed a direct relationship with certain pre-traumatic personal experiences and conflicts which were expressed symbolically in the patient's behavior and attitudes. With considerable personal support by physician and nurse in an accepting hospital environment, improvement was rapid and the child appeared to have completely recovered ten weeks after the accident.

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#### Erratum

In the article by Chute, Robinson, and Donohue, entitled "Cushing's Syndrome in Children," on page 20 of the January, 1949, issue of *THE JOURNAL*, the footnote should read "From the Departments of Pathology and Pediatrics at the University of Toronto and The Hospital for Sick Children, Toronto, Ontario."

## Case Reports

### ACCIDENTAL BENADRYL POISONING: REPORT OF A FATAL CASE

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THE so-called antihistamine drugs have had a wide and rather extensive use in the past few years. Various toxic and undesirable side effects such as drowsiness and dermatitis have been reported from their use, and in a few cases severe toxic symptoms and even death have occurred from marked overdosage.<sup>1</sup> Recently, a 2-year-old child accidentally consumed a quantity of beta-dimethylamino-ethyl benzhydryl ether hydrochloride (Benadryl), which caused his death.

#### CASE REPORT

A. L., a 2-year-old white male child, weight 27 pounds, was seen twenty or thirty minutes after his mother found him consuming the contents of a bottle of Benadryl (25 mg.) capsules. It was later determined that he took nineteen capsules; total dose, 475 mg. When first seen he was lethargic and respirations were shallow. Gastric lavage produced numerous large food particles; strands of partially liquefied pink gelatin could also be identified. The food particles continually plugged the tube and the lavage had to be terminated because of the poor condition of the patient, who was already cyanotic and showing convulsive movements. There was some emesis of gastric contents at this time. Caffeine sodium benzoate,  $2\frac{1}{2}$  grains, was given hypodermically, and the convulsive movements were controlled temporarily by the use of vinyl ether or ethyl chloride inhalations. As soon as enough anesthesia was given to stop the convulsions, the child became very cyanotic; oxygen, on the other hand, seemed to increase the seizures as it improved the cyanosis. Sodium phenobarbital, 2 grains, given over a one-half hour period, had no demonstrable effect. About two hours after onset the rectal temperature was  $102.4^{\circ}$  F. and pulse 110 to 120. He was transferred to the hospital where he was placed in an oxygen tent and given 5 per cent dextrose by elysis. Breathing was very shallow, and at times Cheyne-Stokes in character. He was completely unconscious, moderately cyanotic, and was having clonic convulsive movements of all extremities. The lips were dry, the pupils dilated and fixed. One hundred milligrams of sodium pentothal given intravenously caused some muscular relaxation and the pupils returned to normal size, but there was no real improvement in the child's condition. During the afternoon the temperature gradually rose to a high point of  $107.4^{\circ}$  F. in spite of cool sponges to the body, flushes, etc. The fever then dropped somewhat, but remained the rest of the time between  $102^{\circ}$  and  $105^{\circ}$  F. The extremities, however, were always quite cold to the touch. Respirations became very shallow and the pulse irregular. He was given alpha-lobelin and epinephrine as terminal measures, but the child expired approximately thirteen hours after he had taken the drug.

#### SUMMARY OF AUTOPSY REPORT

Autopsy was performed approximately seven hours after death and after arterial embalming. External examination revealed a well-developed and well-

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nourished male infant measuring 38 inches in length and weighing an estimated 30 pounds. External examination was essentially negative except for slight post-mortem hypostasis of posterior head and trunk, and presence of rigor mortis. Skin was generally clear but for the following exceptions: Recent venipuncture wounds in both antecubital fossae and diffuse swelling of both thighs with tiny puncture wounds anteriorly. There were no surgical scars. Superficial lymph nodes were not palpably enlarged. Trunk and abdomen were not remarkable. Feet were in a position of plantar flexion.

*Internal Examination.*—Subcutaneous fat was bright yellow and averaged 0.7 cm. over the abdomen. Abdominal organs showed the usual positions and relations. Liver edge was 3.5 cm. below the ensiform and 2 cm. below the right costal margin. Thymus was large with two symmetrical lobes, each measuring  $8 \times 4 \times 1.5$  cm. Surface and cut section showed hundreds of tiny purplish-red petechiae. There was no evidence of tracheal deviation or compression. Trachea and larynx contained a small amount of brownish mucoid fluid resembling stomach contents, with similar material in main bronchi and major branches, without gross food particles. Lung borders were separated 5 cm. in the upper midline. Cardiac apex measured 4 cm. to the left of the midline at the fifth rib. There were a few drops of clear fluid in the pericardium. Heart was average in size, and showed about two dozen bright petechial hemorrhages over the epicardial surface of both ventricles posteriorly. The endocardium and valve leaflets were clear and the orifices were not dilated. The foramen ovale was closed. There was a single 2 mm. hemorrhage in one papillary muscle on the left side. The two lungs were essentially normal in size and configuration. There was mottled pinkish-purple discoloration over the posterior pleura on both sides, and cut surface showed confluent areas of red consolidation posteriorly. Frothy fluid could be expressed from the cut surface. Hilar lymph nodes were not enlarged, and pulmonary vessels were clear. Spleen and pancreas were not grossly remarkable. The colon contained soft brownish fecal material. Ileocecal region and appendix were not abnormal. Entire small intestine showed no gross abnormality. Duodenum contained flocculent mucoid fluid. The stomach was not distended or discolored, but was almost solidly filled with partly digested fruit and vegetable fragments mixed with brown fluid. Recognized among these were green berries with stems, bits of cabbage, celery, and apple. No remaining pills or fragments of capsule were found. Stomach mucosa was pale gray and softened, with some loss of mucosal markings. There were two bright red macular areas on the mucosa, without ulceration. Liver and gall bladder appeared grossly normal, except for moderate diffuse congestion of the hepatic parenchyma. Adrenals were average in size and symmetrical with thin yellow cortices. Both kidneys measured about  $8 \times 5 \times 2.5$  cm. and showed a uniform pink cortex averaging 5 mm. and dark red pyramids. Pelves were not dilated but both ureters showed fusiform dilatation in the midportion, averaging 3 to 4 mm. in width against 2 mm. in remainder of the course. Bladder was filled with clear amber urine. Prostate was infantile.

Examination of the head revealed normal scalp and skull. The dura was pale gray and delicate, and lightly adherent to the skull cap. Inner meninges were delicate and translucent, with moderate congestion of the pial veins with dark blood. Hemispheres were symmetrically large with flattening of all convolutions and obliteration of the sulci. No definite cerebellar pressure cone found. On cut section, gray and white matter of the brain were well demarcated, but were soft and almost jellylike. There was slight injection of small vessels in the central white matter, but no focal softening or hemorrhage. Ventricular system was uniformly small and possibly compressed. Basal

ganglia, brain stem, pons, and cerebellum were not grossly abnormal. Pituitary was small and firm. Portion of spinal cord from the dorsolumbar region showed normal caliber and markings on cut section.

*Microscopic Findings.*—The heart showed the usual infantile structure. There were rare perivascular hemorrhages of microscopie size in the deep myocardium, and a larger perivascular hemorrhage in the epicardial fat of the left ventricle. Sections of lungs showed desquamation of bronchial mucosa with normal appearance of the submucosa and peribronchial glands. This suggested digestion by aspirated stomach contents. Lung parenchyma showed diffuse congestion of medium and small vessels, and extensive areas of alveolar edema and hemorrhage. There were a few large phagocytic cells in some alveoli, some of which contained fine carbon pigment. Medium and small bronchi contained a film of adherent leucocytes and granular brown amorphous material resembling bile pigment. There were small colonies of bacteria in the alveolar fluid in a few areas representing probable post-mortem growth. There was no evidence of pneumonia. The thymus showed multiple areas of fresh hemorrhage in the follicles and central pulp. Sections of thyroid, pancreas, and liver showed no significant change. The spleen showed evidence of necrosis in the Malpighian follicles, with amorphous eosinophilic material and granular basophilic fragmentation resembling nuclear debris replacing the central areas. There was acute congestion of the red pulp, but no areas of hemorrhage.

Sections of brain showed a somewhat spongy appearance of the cortical white matter with small clear vacuoles around many of the glial cells. There was a similar appearance in sections through the basal ganglia and wall of ventricle. Sections of pons showed marked increase in the perivascular space surrounding medium and small vessels, with a few areas of diapedesis of red cells. No areas of extensive hemorrhage found. The cerebellum showed no focal change. The Purkinje cells were well preserved.

The spinal cord showed marked perivascular edema surrounding the central vessels with necrosis of near-by nerve substance. This appeared more marked than any change in the brain itself and suggested terminal anoxia.

*Summary of Autopsy.*—Autopsy findings were similar to those in heat stroke with thymic and epicardial petechial hemorrhages, pulmonary congestion and edema, and passive congestion of liver and kidneys. There was evidence of gastric retention of partly digested food and terminal aspiration of gastric fluid in the trachea and bronchi. Findings in the brain were generalized cerebral edema and softening, with congestion of the pial veins. The microscopie findings confirmed the gross autopsy findings, with the addition of acute focal necroses in the splenic follicles, and perivascular necrosis in the spinal cord. Since autopsy was done approximately seven hours after death, and following embalming, the significance of the fine histologic changes were thought to be somewhat open to question. The presence of asphyxial hemorrhages above the diaphragm would suggest some interference with oxygenation, either as a direct effect of the drug, or possibly a result of terminal aspiration during the stage of coma.

#### DISCUSSION

Toxicity studies on animals<sup>2</sup> showed that death was produced in a few minutes to several hours after oral ingestion of Benadryl, and was preceded by violent excitement, convulsions, respiratory failure, and death. The development of hyperthermia is not specifically mentioned. With nonlethal toxic doses there was violent excitement but recovery was complete and prompt. When phenobarbital was given to rats before the administration of Benadryl, the

severe convulsions were prevented, but there was no improvement in the mortality rate. We felt justified in using the barbiturates in this case to control the convulsions even though it meant the use of a sedative drug in conjunction with an agent which itself also produces drowsiness and depression. The manufacturer, we learned later, specifically advises against the use of barbiturates even though convulsions are severe. These recommendations are based on at present unpublished experiments in monkeys where toxic doses of Benadryl and barbiturates were found to be a dangerous combination. The active measures of treatment that were recommended include evacuation of the stomach and gastrointestinal tract, hydration by all practical routes, and the encouragement of elimination through the skin by the application of warmth. Considerable effort has been expended in trying to find a specific antidote for the drug, but so far this work has been completely unsuccessful.

The fatal dose in our patient, 474 mg., or approximately 43 mg. per kilo., of which an unknown portion was eliminated by gastric lavage, is somewhat less than that found for experimental animals. The LD-50 for rats by the oral route was 545 mg. per kilo, and for intravenous administration, 45.7 mg. per kilo. In dogs, the LD-50 for intravenous administration is 30 mg. per kilo.

Finally, it seems worth while emphasizing the technical difficulty that sometimes attends the emptying of a child's stomach. The pieces of food, berries, etc., were so large that they could not be brought up by any stomach tube, and the child was so drowsy and depressed when first seen that it was impossible to make him vomit effectively.

#### SUMMARY

The accidental ingestion of 474 mg. of Benadryl by a 2-year-old child resulted in cyanosis, convulsions, cardiorespiratory depression, hyperthermia, and death. Autopsy findings were similar to those of heat stroke with petechial hemorrhages and cerebral edema. No specific antidote for Benadryl toxicity has been developed; symptomatic measures are discussed.

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## POTASSIUM BROMATE POISONING: REPORT OF A CASE DUE TO INGESTION OF A "COLD WAVE" NEUTRALIZER

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POISONING due to potassium bromate, a toxic inorganic salt, is rarely encountered and only two case reports have come to our attention, one of which<sup>1</sup> was similar to the case to be reported, and presented necropsy findings. This substance is used as the neutralizing solution in the "cold wave" home permanent process; according to the manufacturer it is a necessary part of the process and to date no adequate substitute has been found. It is to be expected that the number of cases of poisoning due to potassium bromate will be increased along with the widespread use of this permanent wave process in the home. In order that the medical profession be fully aware of its toxic potentialities the following case is reported.

### CASE REPORT

M. L. N., a 2½-year-old white boy, was admitted to the Tucson Medical Center at 9 P.M. on June 18, 1948. He had drunk approximately one-half glass of the neutralizing solution of one of the cold wave processes eight hours previously. One hour after ingestion he vomited and was taken to another hospital where the stomach was lavaged with sodium bicarbonate. The child was discharged from that hospital but continued to vomit every one-half hour. At approximately 3 P.M. diarrhea ensued and up until the time of admission there were five loose, watery stools. The child had urinated several times and "the lips seemed blue." At 8 P.M. the temperature had risen to 101° F., and one of us (H. C. T.) was called, and the child was admitted to the hospital for treatment.

No previous history of kidney disease could be elicited.

On admission this well-nourished, well-developed child was extremely irritable but was otherwise not physically remarkable. There was no cyanosis. The blood pressure on admission was normal (96 systolic, 54 diastolic) and remained so throughout his entire course. The admission temperature was 100.2° F.

For the first twelve hours the child had no emesis and retained fluids by mouth. There was a yellow, semiformal stool with mucus and involuntary voiding of a small amount of urine. A dry, hacking cough developed.

The morning after admission the child vomited and was maintained for about eight hours on rectal fluids, following which infusions of 5 per cent glucose in Ringer's lactate were given.

It was noted on June 19 at 4:30 P.M. that the child had not voided since 4:30 A.M. Catheterization failed to obtain any urine. The child was increasingly restless and was vomiting every twenty to forty minutes. At 11:20 P.M. twitching movements of a few seconds' duration were noted in the right arm and leg, and by 11:45 P.M. the twitching motions were generalized and shortly thereafter became true convulsions lasting for about three minutes. These recurred every twenty to thirty minutes and by 1:30 A.M. were continuous despite heavy sedation and a lumbar puncture. Except for a few minor episodes, convulsions ceased until 3 A.M., when a generalized convulsion

of forty-five minutes' duration occurred. To combat anuria and prevent any dehydration by vomiting intravenous fluids were given. Failure to promote diuresis with these measures led to the use of 4 per cent sodium sulfate solution, reputed to be of value in these instances.

By 8 A.M. on June 20, edema of the face, hands, and feet was developing and the child was vomiting at fairly frequent intervals. By 6 P.M. the edema was generalized although ascites or pleural effusion did not develop. Anuria persisted from 4:30 A.M. on June 19 until 4 A.M. on June 20, when the child voided 90 c.c. of urine during one of his convulsive periods, following which he was again anuric. At 11:45 P.M. on June 21, 100.0 c.c. of hypertonic plasma were given intravenously and the dextrose and Ringer's lactate solutions continued as before. At 1:45 A.M. on June 21, two hours after the plasma had been given, the child voided 60 c.c. of urine and by 7 A.M. had voided 210 c.c.

Following the termination of the anuria the child progressively improved. Emesis became less frequent, the edema gradually diminished, and the urinary output increased until the child voided 750 to 1,000 c.c. on June 23.

The child was discharged on June 25 and when last seen on August 8 was well and happy. A previously noted anemia was still present. That there might still be some impaired renal function was evidenced by a total PSP excretion of 55 per cent in the one-hour volume of 250 c.c. of urine.

*Laboratory Examinations.—*

(See Tables I and II.)

TABLE I. URINALYSES

DATE	SP. GR.	ALBUMIN	W.B.C./HPF	R.B.C./HPF	CASTS/HPF
6-20	qns	3+	"loaded"	3-4	3-4
6-21	1.009	1+	10-15	occ.	12-15
6-23	1.004	trace	100-125	occ.	12-15
6-24	1.009	trace	60-75	0-1	few hyaline
6-25	1.005	trace	60-70	0-1	few hyaline
7-6	1.021	negative	4-6	0	0

TABLE II. BLOOD EXAMINATIONS

DATE	R.B.C. (MILLIONS)	HGB (GM.)	W.B.C.	NPN	PROTEIN (GM.)	PSP
6-19	3.90	11.4	15,500	86	—	—
6-20	—	—	—	118	—	—
6-21	—	—	—	114	—	—
8-6	3.48	10.7	3,600	34	7.7	55%

*Treatment.*—Therapy consisted mainly of sedation with 50 per cent magnesium sulfate, sodium phenobarbital, and chloral hydrate as indicated. Fluids consisted of an alternation of 5 per cent dextrose in normal saline, 5 per cent dextrose in distilled water, and 5 per cent dextrose in Ringer's lactate. The saline was discontinued when edema was noted. A solution of 4 per cent sodium sulfate was given intravenously to promote diuresis. Hypertonic plasma, prepared by dissolving lyophilized plasma with one-half the usual diluent, was given as another diuretic measure. Two hours after that had been given urinary excretion returned, but whether the sodium sulfate or the plasma was responsible cannot be determined.

#### DISCUSSION

Potassium bromate is almost unknown to the medical profession and is infrequently mentioned in textbooks of pharmacology and toxicology. It is similar to potassium chlorate but is estimated to be twenty to thirty times

as toxic for experimental animals.<sup>2</sup> Neither the chlorate nor the bromate ion is destroyed to any extent by the body, but both are absorbed from the gastrointestinal tract and excreted slowly by the kidneys almost in toto. These salts produce gastrointestinal irritation as evidenced by vomiting, cramping abdominal pains, and diarrhea. Absorption of the chlorate ion into the blood has produced destruction of erythrocytes and methemoglobinemia in experimental animals. This is probably not true for the bromate ion, though there is some evidence that it produces hemolysis in guinea pigs.

The slow, prolonged, renal excretion is probably a direct cause of the acute and subacute nephritis. In the case reported by Dunsky the necropsy findings revealed a predominance of tubular lesions while the glomeruli were almost uninvolved. The lesions were diffuse but he did not consider that they were an adequate explanation for the anuria in his case.

With the widespread use of home permanents—the number runs into the millions each year—and the fact that children are very liable to drink this colorless, almost tasteless solution, and that no antidote for potassium bromate apparently was known, the Toni Company, which manufactured the home wave sets, was contacted, as well as *Parents' Magazine*, whose Consumer Service Bureau had approved the process. The Toni Company sent a representative to investigate and it has been learned that research is in progress to determine antidotes for this poison. The research pharmacologist<sup>3</sup> suggested that the stomach acidity be neutralized to prevent the formation of the irritating hydrobromic acid and that a sodium salt be used to counteract "the toxic effects of potassium ion or substitute sodium bromate for potassium bromate." He also suggested the use of sodium thiosulfate to combat the oxidizing effect of the bromate ion.

The Toni Company representative<sup>4</sup> also states that the company is changing the format of the neutralizer package to emphasize more clearly the toxic nature of the product, and is also changing the directions for use so that the solution will not be allowed to stand around the house of the user for several hours.

#### SUMMARY

A case of potassium bromate poisoning due to the ingestion of a neutralizer solution used in one of the cold wave home permanents has been reported. The case was marked by protracted vomiting, diarrhea, convulsions of several hours duration, and anuria with azotemia. Treatment included the use of 4 per cent sodium sulfate and hypertonic plasma as diuretics. Recovery followed and the child is now living and well. The use of sodium thiosulfate as an antidote has been suggested.

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## NEUROBLASTOMA (SYMPATHOGONIOMA) OF THE ADRENAL IN A NEWBORN INFANT

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A NEGRO female newborn infant died nine hours after delivery. Pregnancy and delivery were not unusual. Following delivery the baby had respiratory difficulty and was noted to be cyanotic. On admission to the Babies and Childrens Hospital shortly after birth, temperature, pulse, and respiratory rate were normal. The abdomen was greatly distended by a mass filling the epigastrium and both flanks, extending 3 cm. below the level of the iliac crests. Examination of the blood revealed 28,800 leucocytes per cubic millimeter and 30 per cent erythroblasts. The child died despite oxygen and stimulants.

Autopsy disclosed a neuroblastoma of the right adrenal with metastases to the liver, parapancreatic lymph nodes, and left adrenal. The liver extended 9 cm. below the costal margin in the right midclavicular line, displacing the intestines dorsally and inferiorly and elevating the diaphragms to the level of the fifth ribs bilaterally. The organ weighed 425.5 grams as compared with an average expected weight of 78 grams. The outer surface was nodulated by slightly projecting rounded masses, 3 to 8 mm. in diameter. In the cross section most of the liver was replaced by well-defined, generally circular, pale gray, slightly bulging, relatively soft, slightly moist nodules, variable in size and measuring from 3 to 5 mm. in diameter.

The right adrenal and tumor weighed 83.5 grams as compared with an average expected weight of 2.7 grams for the adrenal. It was attached to but did not invade the kidney. It displaced the right kidney dorsally and inferiorly and the duodenum ventrally and inferiorly. The tumor was lobulated, soft, and red. Penetration of the capsule was obvious. The left adrenal weighed 6.0 grams and contained several tumor nodules about 5 mm. in diameter.

Microscopically, the tumor is somewhat lobulated by fairly heavy bands of mature connective tissue richly supplied with capillaries. Most of the tumor cells are about the size of a lymphocyte, with dense nuclei and scanty cytoplasm. Some cells are slightly larger, with vesicular nuclei and a fair amount of cytoplasm. A few cells are multinucleated but there are no mitotic figures. Delicate fibrils are numerous and do not stain by the phosphotungstic acid method. There are many pseudorosettes with a centrally disposed mesh of fibrils surrounded by rims of tumor cells. There are numerous small hemorrhages and a few foci of necrosis. In the metastases the cell-type is the same but lobulation is not distinct, connective tissue is not rich, vascularity is not great, fibrils are not numerous, and pseudorosettes are scanty. The small size of the cells of the tumor and the numerous fibrils in the adrenal tumor justifies classification as sympathogonioma rather than sympathoblastoma.

### COMMENT

This case is unusual in that the tumor was obviously present during gestation. Neuroblastoma is a common tumor in the first decade of life, exceeded in frequency only by the leucemias and by embryonal carcinoma of the kidney, but it is rare at birth. An instance has been reported of its occurrence in a

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28-week fetus,<sup>1</sup> and one of fetal dystocia due to widespread hepatic metastases in a term infant.<sup>2</sup> It must be borne in mind in the diagnosis of hepatomegaly at birth since other diseases characterized by large liver, such as erythroblastosis fetalis and Gaucher's disease, rarely cause great enlargement of the liver until at least several hours after delivery or later.

There are two main types of metastasis: To the liver, which is said to occur in younger patients (average age  $1\frac{1}{2}$  years); and to the osseous system, particularly the orbit and calvarium, which is said to occur in older children (average age 3 years).<sup>3</sup> The two types are frequently present in the same patient and have neither clinical nor prognostic importance; thus the differentiation into "Pepper" and "Hutchinson" types of disease, and the attempt to predict the side of the original lesion on the basis of its metastases as has been done in the past is not justified.<sup>4</sup> The common presenting symptoms, then, are a mass in the abdomen, exophthalmos, or tumor of the skull. The primary tumor is rarely noted either by the patient or the parents. Frequently the diagnosis may be suggested by destructive lesions in the typical bony locations. The tumor is moderately radiosensitive<sup>5</sup> but almost invariably fatal within a year from the onset of symptoms.

#### SUMMARY

This is a report of clinical and post-mortem observations on a Negro female infant who died nine hours after birth with a large neuroblastoma of the right adrenal which had already metastasized to the liver, parapancreatic lymph nodes, and left adrenal. The microscopic features indicate that the tumor is a sympathogonioma, the most primitive form of neuroblastoma.

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## GASTROESOPHAGEAL INTUSSUSCEPTION

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**I**NTUSSUSCEPTION is the commonest cause of acute intestinal obstruction in children. It is primarily a disease of infancy, 80 per cent of cases occurring in the first two years of life and 50 per cent between 5 and 7 months of age. However, retrograde intussusception or invagination of the bowels from below upward is a rarity. There are only scattered case reports in the literature, and the diagnosis is usually made at operation or post mortem.

The following report is unique since not only was there a retrograde intussusception but in addition the stomach, which is rarely involved, was the site of the intussusception.

### CASE REPORT

G. W., a 16-month-old Negro child, was admitted to Harlem Hospital on Dec. 8, 1946, with a history of waking during the night gagging and vomiting bright red blood. For supper the child had mashed potatoes and milk. As far as the mother knew no foreign bodies, medications, or corrosives were accessible to the child.

*Past History.*—The child had no previous serious illnesses. He had had a circumcision two weeks previous which was uneventful.

*Physical Examination.*—Physical examination revealed a well-developed and well-nourished male child who appeared somewhat sleepy and who was very comfortable except for intervals when he vomited copious amounts of mucus mixed with bright red blood. There were no bleeding points seen in the nose, mouth, or pharynx. The abdomen was soft, no masses were felt, and no tenderness was elicited, spleen and liver were not enlarged, and x-ray of the stomach and esophagus revealed no evidence of foreign body. Lungs were reported as negative.

*Laboratory Data.*—Red blood cells were 4.23 millions; hemoglobin 13.9 Gm.; white blood cells, 9,600 with 89 per cent polymorphonuclears, 3 per cent stabs, one per cent eosinophile; sickling preparation, negative; hematocrit, 52.2 per cent; specific gravity of blood 1.064. Temperature varied between 98 and 99.2° F. Pulse was 108 to 112, respirations, 24. To maintain water and electrolyte balances continuous clyses were given.

The child remained comfortable throughout the first and part of the second hospital day. Vomiting of bright red blood ceased after the first day and the only evidence of hemorrhage was a few small, dark brown spots seen about the bed sheet. Despite the infrequent vomiting on the second hospital day and the administration of continuous clysis, dehydration became quite pronounced. Toward the end of the second hospital day the child suddenly developed acute respiratory distress and expired within thirty minutes after this acute episode.

An autopsy was performed.

*Gross Pathological Diagnosis.*—Diagnosis was: (1) Intussusception of antrum of stomach into midesophagus with gangrene of intussusception and high intestinal obstruction; (2) acute passive congestion of lungs, liver, and

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splanchnic bed; (3) dehydration; (4) moderate fatty change of liver; (5) marked mesenteric lymphadenopathy. In the posterior mediastinum the esophagus at its midpoint is seen to balloon out suddenly to 2.75 cm. in diameter from the usual 1.25 cm. Palpation reveals it to be slightly boggy and firm. The dilatation continues to the stomach. The esophageal hiatus is free of defects and is bound in its usual tight manner to the wall of the esophagus. The stomach is invaginated by its central portion which apparently has traversed the stomach



Fig 1—Anterior view a, Greater curvature of stomach b, Knuckle of stomach c, Liver d, Esophagus with intussusception



Fig 2—Anterior view after opening of esophagus a, Liver. b, Esophagus c, Intussusceptum d, Greater curvature of stomach

and now rests in the esophagus in an extensive intussusception. The first portion of the duodenum is slightly redundant, the remaining portions normal. The remaining bowel does not appear unusual.

The stomach presents the picture of marked intussusception of the antrum into and as far as the midesophagus. There is as a result a knuckle of stomach which extends about the intussusception from anterior to posterior aspects of the body of the stomach. The cardia, fundus, and greater curvature of the stomach are not involved in the intussusception. The lesser curvature and adjacent stomach and the lower half of the esophagus act as the intussusceptions. The pylorus is drawn up somewhat by the intussusception from its usual level at the first lumbar segment. There is no diaphragmatic herniation other than the intussusception. The duodenum is in its normal anatomical position except for slight upward movement of the first portion with the pylorus. The gastrocolic, gastrohepatic, and gastrosplenic ligaments are all without defect.

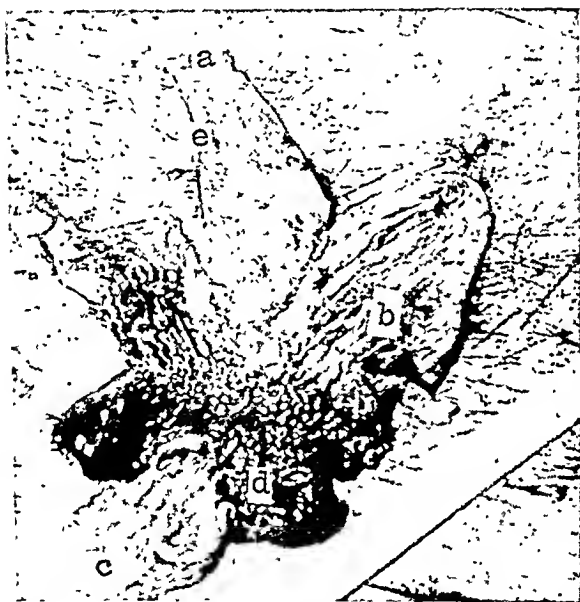


Fig. 3.—After dissection of esophagus, stomach, and pylorus. *a*, Esophagus. *b*, Antrum of stomach. *c*, Pylorus. *d*, Area intussuscepted (hemorrhagic). *e*, Esophagus with red area (where intussusceptum rested).

#### COMMENT

The normal difference in diameters between the small and large bowel and the course of peristaltic waves from above downward favor isoperistaltic intussusception. Occasionally, however, some local condition such as a tumor mass, Meckel's diverticulum, edema at the site of a gastrojejunostomy, a gastric diverticulum, chemical irritation, or even great abdominal distention may so alter conditions as to cause reverse peristalsis and make lumen of the small intestine relatively larger than that of the large bowel, thus producing a retrograde type of intussusception.

The case reported is unusual inasmuch as the stomach was the site of the intussusception and no visible pathogenetic factors were found to account for the development of a retrograde type of intussusception. The stomach is involved in an intussusception rarely, as a review of the literature indicates



1, 2, 4-9. The stomach is invaginated less often than the intestine because (a) it is well fixed at both curvatures, (b) its lumen decreases in the direction of the peristaltic movement, and (c) there are no wandering rings of contraction as in the intestines. The reported cases of intussusception of the stomach revealed predisposing etiologic factors in the majority of instances. Desternes and Baudon<sup>1</sup> found marked gaseous distention of the abdomen to have produced invagination of the stomach in their case. At operation a perforation of the stomach with adhesions to the liver was found. Cure followed surgical intervention. A polyp of the stomach was found by x-ray to be the cause of invagination in some of the reported cases,<sup>5, 6, 8</sup> and found on post mortem in another instance.<sup>2</sup> A diverticulum of the greater curvature was the point of origin of a gastroesophageal invagination as reported by Liaras and Ricard.<sup>7</sup> The stoma of a gastrojejunostomy was the site at which an inversion of the stomach occurred in another case report.<sup>9</sup> Experimentally it has been shown that the application of a mixture of .01 per cent silver nitrate plus 15 per cent sodium nitrate to the antrum of a dog's stomach caused edema of the area irritated and a retrograde gastrogastic intussusception resulted. Lannon and Culiner<sup>4</sup> reported the case of a 3- to 4-year-old child with a history of hematemesis and one that simulates our own case in almost every respect. On post mortem they found a retrograde intussusception of the lesser curvature, pylorus, and first part of the duodenum into the esophagus.

#### SUMMARY

This is a report of a case of retrograde intussusception in a 16-month-old male infant in whom the pyloric end of the stomach was invaginated into the esophagus. The outstanding symptom was hematemesis. Despite the decrease in vomiting and the use of parenteral fluids, there was a continuous downhill course associated with an unrelieved high intestinal obstruction. At post mortem no etiologic factors were found which could have induced the development of this type of intussusception. The literature on cases of retrograde intussusception involving the stomach is reviewed and this case is an addition to the few cases reported.

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# Psychologic Aspects of Pediatrics

## CEREBRAL DAMAGE AND BEHAVIOR DISORDERS IN CHILDREN

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WITHIN recent years there has been a growing appreciation of the multiplicity of factors, both endogenous or individual and exogenous or environmental, which may cause disturbances of behavior in children. The current trend was forecast in 1938 by Lurie,<sup>1</sup> who decried the then prevalent attitude of attributing all disorders of behavior to "suppressions, frustrations, rejections, identifications, feelings of hostility, feelings of inferiority and inadequacy and the like." A breakdown by Lurie of the cases seen at the Child Guidance Home in Cincinnati showed that in 49 per cent of the behavior disorders studied there the underlying causative factors were endogenous or psychophysical in origin. In 28 per cent of the cases both endogenous and exogenous factors were operative, and in only 23 per cent were the causes primarily exogenous or environmental.

That cerebral damage of so mild a degree as not to give gross changes in motility or in the reflexes may, nevertheless, be the basis for disturbances of behavior in a certain number of children, is of special interest to the pediatrician. The causes of cerebral damage, encephalitis, head injuries, anoxia, etc., are conditions which we, not the psychiatrists, are called upon to treat; the symptoms of disturbed behavior are fairly characteristic; and the treatment is within the scope of the pediatrician.

The frequency with which cerebral damage and behavior disorders in children are related has not been estimated accurately but apparently it is not great. According to Bender<sup>2</sup> only from 2 to 5 per cent of the highly selected group of difficult problems sent to the Children's Observation Ward of the Psychiatric Division, Bellevue Hospital, are due to inflammatory encephalitis, and about 2 per cent more are related to head injuries. The incidence of postencephalitic behavior disturbances at the Child Guidance Home in Cincinnati is about 3 per cent. How often other types of cerebral damage are associated with behavior disturbances is not known.

### ETIOLOGY

Behavior disorders have been observed with cerebral damage due to encephalitis, burns, head injuries, brain tumors, cerebral anoxia, and allergy. In addition, a large number of organic disorders of the brain may present themselves as behavior disturbances, e.g., myoclonic epilepsy, tic (Gilles de la Tourette), narcolepsy, tuberous sclerosis.

Encephalitis.—Changes in personality and behavior occur in a large percentage of all children following encephalitis. The symptoms generally become

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apparent immediately after the acute phase of the disease is over, although their appearance may occasionally be delayed for years. According to Ford,<sup>2</sup> in children under 3 years of age mental development is often completely arrested and imbecility or idiocy results. Children between 3 and 10 years of age show no striking reduction in mental capacity or evidence of gross neurologic disease but there may be marked aberrations in personality and behavior. The children are impulsive and destructive. They respond to the impulse of the moment without thought of the consequences. Undeterred by natural inhibitions or fear of punishment, they may lie, steal, destroy property, set fires, and commit sex offences. They make no effort to escape detection and, when asked about their misdeeds, they say that they could not help it. Although they show remorse which is often exaggerated, they continue to misbehave. They are, as a rule, indifferent to punishment.

The mood changes quickly. Sudden outbursts of temper may occur without any reason, during which the child may inflict physical harm on the persons about him. Depression, elation, and manic states are often seen. Some children show excessive and precocious sex interest.

A prominent feature of the postencephalitic child's behavior is hyperkinesia. The child is always on the go. Nocturnal insomnia and reversal of the normal sleep rhythm are commonly associated with the overactivity. Despite the apparent fearlessness, the children are often subject to night terrors and fears of imaginary persons. Older children may develop hypochondriasis.

Greenebaum and Lurie<sup>4</sup> describe the postencephalitic child as, characteristically, hyperactive, restless, and destructive, with a short attention span, highly distractible, lacking in self-control, and extremely unpredictable in his actions.

*Burn Encephalopathies.*—Generalized degenerative changes in the brain have been observed in association with extensive burns.<sup>5</sup> The clinical manifestations are those usually seen in children with diffuse cerebral damage, hyperkinesia, poorly patterned behavior, and inability to adapt to social demands. There is some interference with mental functioning which may be progressive. School adjustment is poor.

Behavior deviations associated with the cerebral damage should be distinguished from personality changes which result from the child's reaction to his prolonged hospitalization and to his disfiguring scars.

*Head Injury.*—Children withstand head injuries better than adults, among whom the presence of arteriosclerosis would seem to predispose to more serious damage.<sup>6</sup> In most instances psychic disturbances appear some time after the injury but occasionally there is an immediate reaction manifesting itself as an acute psychosis with excitement, marked impulsiveness, and restlessness over which the child has no control. Irritability and anxiety are prominent features. The children are amnesic from the accident but their memory is otherwise unimpaired and they are able to recognize parents, physicians, attendants, etc. normally. The psychosis lasts from two to five weeks and recovery is generally complete without sequelae.

The posttraumatic chronic disturbances may take the form of (1) a behavior disorder, (2) epilepsy with secondary deterioration, or (3) cerebral defect with secondary intellectual deterioration.

Behavior disturbances generally occur after severe trauma but they may follow apparently minor injuries. The syndrome resembles closely that of the postencephalitic. Though the personality changes appear shortly after the injury, the child may not come under observation until several years later. When the injury takes place during the preschool years the child's misbehavior is often tolerated at home and he is brought to the physician only after he starts to go to school and begins to get into trouble there.

The behavior disturbance is characterized by unusual changes in personality, the outstanding features of which are overactivity, restlessness, destructiveness, impulsiveness, assaultiveness, cruelty to animals, emotional instability, temper tantrums, trunancy, and delinquency. There is no loss of mental power.

Posttraumatic epilepsy is a late complication and is sometimes susceptible to surgical treatment. Since convulsions occur only rarely after severe head injury, it is assumed that a constitutional predisposition is required. Ford<sup>7</sup> estimates that approximately 2 to 3 per cent of all cases of epilepsy are related to injury sustained at birth. Posttraumatic epilepsy in children frequently leads to secondary changes varying from mild personality disorders to marked mental and affective deterioration.

Posttraumatic mental defects are rare. They include the various forms of aphasia, defects of memory, and loss of intellectual power.

In evaluating the role of cerebral damage due to head injury, the possibility of a predisposing condition must always be kept in mind. Of eighty-six children who manifested behavior disorders associated with head injury, Fabian and Bender<sup>8</sup> found predisposing conditions in about one-fourth. Eight children were mentally retarded, five were epileptic, six suffered from some preceding type of brain damage, and two were psychotic. Fabian and Bender believe that "accident proneness" was an important factor leading to mishaps in their patients. The majority of their children came from a highly traumatic environment in which the parents were either alcoholic or were suffering from psychopathologic disorders.

*Brain Tumors.*—Disorders of behavior and personality associated with brain tumor are somewhat less frequent in children than in adults, owing, probably, to the rapidity with which tumors in children go on to produce definite signs of increased intracranial pressure and local damage.<sup>9</sup>

Keschnner, Bender, and Strauss<sup>10</sup> described the disturbances in behavior of children with brain tumor. Of thirty-seven children under 14 years of age, approximately one-third showed personality changes. The most frequent manifestations were apathy, dullness, somnolence, poor cooperation, and inattention of a mild or transitory nature. In addition there were apprehension and depression, excessive crying, and temper tantrums. One child showed euphoria. In five, nonspecific personality changes were observed; that is, the parents described the children as "different persons."

Langford and Klingman<sup>11</sup> described three children with intracranial tumor, two of whom had posterior fossa tumors, one a craniopharyngioma. The most

frequent symptoms were anorexia, regressive behavior (a desire to be babied and waited on, jealousy not present before), listlessness, and withdrawal of interest from normal occupations. All three children were overanxious. They did well on psychometric examinations.

*Cerebral Anoxia.*—Cerebral anoxia, as a cause of cerebral damage during early life, is receiving increasing attention. In the adult, severe anoxia, whether from asphyxia by smoke, inhalation of carbon monoxide, gaseous anesthesia accidents, strangulation, or depressed respiration produced by drugs, leads to character change and memory defect. Schreiber<sup>11</sup> states that "with the knowledge that the specialized cells of the brain are identical in function in the infant, child, and adult, it is reasonable to assume that asphyxia produces analogous pathologic changes, possibly more destructive, in the younger tissue."

Windle<sup>12</sup> compared the behavior of guinea pigs in whom anoxia had been induced at or close to term by clamping the uterine vessels, with the behavior of littermates who had been delivered (through an abdominal incision) immediately before the induction of asphyxia. He observed that asphyxial conditions during birth produce severe changes in the central nervous system of the guinea pig. In general, the longer the duration of anoxia the more severe were the alterations, although the correlation was not as close as might be expected. In some animals asphyxia of even short duration led to changes, while in others prolonged asphyxia had only a slight effect.

Among the immediate effects encountered were decerebrate states, hyperkinesia, tremors, convulsive seizures, choreoathetoid movements, spasticities, paralyzes, ataxias, somnolence, and impairment of sensory functions. As a rule the neurologic symptoms did not persist in marked form and were only transient. Many of the animals were inferior to their littermate controls in the maze tests. None was superior.

Schreiber<sup>11</sup> has found asphyxia to be the most common cause of cerebral damage associated with traumatic birth. Though the fetus and newborn, in the human as well as other animal forms, can survive degrees of anoxia that would be fatal in later life, the survival does not guarantee freedom from serious damage to nervous structure. Indeed, survival may be a mixed blessing.

In 1945 Preston<sup>13</sup> reviewed the histories of 132 children who had been anoxic at birth. One-fourth of these were mentally retarded. The remainder were of normal mentality but all showed deviate behavior. About 40 per cent of them were hyperactive, approximately the same percentage were apathetic, and about 20 per cent were epileptic.

Feeding difficulties were common during the early months of life and, as a consequence, the children were small and thin. Motor and speech development took place at the expected age, as well as bowel and bladder control. During the runabout age, sleep disturbances were common, the hyperkinetic children sleeping too little, the apathetic ones sleeping too much. Distractibility became evident at this age. Speech impurities and stuttering were common and memory was poor. Social contacts with other children were difficult to establish since the afflicted children were unable to conform to group play and suffered continual frustration. At school the early years were a tragedy, especially for the

bright children, since they were unable to concentrate and to cooperate in school-room routines.

On the whole there appeared to be a retardation in personality development, the school age child behaving like a runabout and the runabout like an infant. The hyperactive children developed an undesirable aggressiveness while the apathetic ones usually avoided conflicts with the world by excessively submissive behavior. At home the children demanded extra attention and as a result many of them were rejected. With the approach of adolescence, often earlier, there was a tendency toward improvement, in some instances complete.

In a recent report Stevenson<sup>14</sup> reviewed the records of 226 unselected children who are being followed in the Department of Maternal and Child Health of the Harvard School of Public Health by Dr. Harold Stuart and his group. He found a significant correlation between the physical condition of the newborn infant and his adjustment to his environment in later childhood, the children who had been in a poor state after birth showing a much higher proportion of poorly adjusted members than those whose condition had been good.

*Pertussis.*—The frequency of neurologic complications following pertussis was recently emphasized by Litvak and associates.<sup>15</sup> Forty-seven out of 6,002 children (0.8 per cent) admitted to the Kingston Avenue Hospital for Communicable Diseases showed gross neuropathy. One-half of the afflicted children were under one year of age, and this is the usual experience. The incidence of cerebral complications in this early group was about 2 per cent.

Lurie and Levy<sup>16</sup> observed definite behavioral, intellectual, and personality changes in thirty-four out of fifty-eight children who had had whooping cough during the first two years of life. The majority of the children first manifested their difficulties between the ages of 10 and 11 years, although in some the onset was even later. The etiologic relationship to pertussis was inferred from a thorough study and evaluation of all the physical, social, emotional, intellectual, constitutional, and hereditary factors that directly or indirectly might have had a bearing on the problems presented by the children. In many instances the developmental histories of the children indicated the sequential relationship between the attack of whooping cough and the retardation in their physical and mental growth. Twenty-five of the fifty-eight children in their group showed clinical signs of gross neurologic disease. Fifteen of the patients showed nerve deafness. Ten were definitely feeble-minded.

A characteristic type of behavior disorder was not observed. A striking finding was a delay in the time of walking and talking. Seventeen of the thirty-four afflicted children showed extreme motor restlessness and impulsiveness with a tendency to destructive and unpredictable behavior.

Preston,<sup>13</sup> in her report on anoxic injury to the brain in early life, mentioned pertussis as the prime cause of anoxia in a number of her children with behavior disorders.

Rosenfeld and Bradley<sup>17</sup> have observed a characteristic clinical picture in a considerable number of children who had had pertussis during the first four years of life (i.e., before the fourth birthday). They attribute the behavior

disturbances to cerebral injury associated with the anoxia during the spasms. A similar clinical picture was observed in a group of children who had a history of difficult resuscitation at birth.

A variety of morphologic changes has been found in the brains of children dying of pertussis with cerebral complications. Hemorrhages are sometimes present. They are, however, usually not of sufficient extent to explain the symptoms. Inflammatory processes have been described but, according to Ford,<sup>18</sup> they are not consistent enough to justify a diagnosis of a true pertussis encephalitis. Widespread degeneration of the nerve cells in the cerebral cortex has been observed by a number of workers. In some patients with cerebral complications no morphologic changes in the brain are found. Hiller and Grinker<sup>19</sup> described a case in which the lesions were identical with those seen in carbon monoxide poisoning.

Cerebral damage in infants was the subject chosen by Dr. Harold Faber in 1947 for his presidential address before the American Pediatric Society.<sup>20</sup> The group which he studied were children in whom the presenting symptoms were mental deficiency, spastic paralyzes, and convulsions. Cerebral atrophy was demonstrated by air encephalogram. In about one-third of his group the probable causative or contributory event took place before birth. In about 40 per cent the traumatic episode occurred in association with the birth process and in about 25 per cent the injury was postnatal. Faber considers the most important traumatic factor to be anoxia. It is his opinion that better obstetrics and better pediatrics could have prevented a considerable part of these disasters if present-day knowledge had been applied.

*Allergy.*—The view that disturbances of behavior may be etiologically related to the allergic process is favored by a large number of allergists and psychiatrists. The relationship was first suggested by Hoobler in 1916.<sup>21</sup> In 1922 Shannou<sup>22</sup> pointed out that allergic children were often restless, irritable, unruly, peevish, out-of-sorts, high-strung, and difficult to manage. He concluded that many of these symptoms result from irritation of the nervous system because of anaphylactic reactions to food proteins to which the patient is sensitized. Rowe<sup>23</sup> and others have stressed the changes in personality and behavior in allergic children. Randolph<sup>24</sup> emphasizes the relation of chronic food allergy to disturbances of behavior. In his experience the foods most commonly implicated are wheat and corn, although any food ingested repeatedly may be the offender.

Stevenson and Alvord<sup>25</sup> recently reviewed the subject of allergy in the nervous system. They concluded that allergic manifestations in the central nervous system may be produced by ingestion of food, inhalation of pollen, injection of serum, or vaccination against bacterial or virus diseases or as complications of various diseases. Experimentally a meningoencephalomyelitis, sometimes with disseminated foci of demyelination, can be produced in ways strongly suggestive of allergy.

The clinical manifestations fall into two groups, (1) chronic fatigue, sluggishness, depression, and (2) instability, fretfulness, hyperkinesia, and hyperexcitability. The affected children are inclined to be unhappy at home and at school. School work is poor because of distractibility and impairment of mem-

ory. The children are generally looked upon as "nervous." Clinical evidence of allergy usually accompanies the psychic changes, but in some instances the disturbances in behavior may be the sole clinical manifestation. According to Randolph<sup>24</sup> removal of the offending foods from the diet results in improvement in behavior.

#### SYMPTOMATOLOGY

The symptoms of cerebral damage, whatever the etiology, are fairly uniform and characteristic. A prominent feature is hyperkinesis or hypermotility. The child is always on the move, touching objects, manipulating them, destroying them. The hyperkinesis leads the child, further, to seek continually to make contact with persons by clinging and overaffectionate behavior, by attention seeking, by nagging, and by abusiveness.

The mood varies unpredictably. Explosive outbursts of anger may occur without any apparent cause. Such reactions resemble the "sham rage" of Bard<sup>25</sup> which has been produced in animals by operations designed to release the hypothalamus from cortical control.

Children with cerebral damage are impulsive. The impulse of the moment is immediately translated into action without thought of the consequences. The children lie, steal, set fires, destroy property, and commit sex offences without apparent benefit to themselves and without regard to the consequences.

The attention span is short and the children are readily distractible. School work is likely to be poor for a number of reasons. Memory is variable, the child learning rapidly on some days, then seeming to forget everything he has learned on other days. There is inattentiveness and difficulty in adapting to the school room. Performance in arithmetic is especially poor.

Gesell and Amatruda<sup>27</sup> speak of a type of injury at birth which expresses itself in speech difficulties, notably stuttering, poorly defined unilateral dominance, and delayed integration. Later serious difficulty in learning to read may become evident. Oculomotor incoordination (e.g., strabismus) and visual defects are frequently associated symptoms.

*Neurologic examination:*<sup>28</sup> The usual signs of neurologic disease such as gross motor disability and changes in the tendon reflexes may be entirely absent. Postural and motility tests, however, often disclose significant alterations.

Evidence of organic brain disease may be elicited by observing the child in the standing position with the arms outstretched in front of him and the eyes closed. Attention should be paid to choreoathetotic movements of the hands and convergence or divergence of the hands, which indicate extrapyramidal involvement; spreading of the fingers, which is a sign of cerebellar disease; or a consistent lowering of one arm, which is indicative of muscle weakness (the dominant arm is generally held a little higher than the other). Having the child count while standing with the arms extended minimizes voluntary compensation for minor defects.

The child's motility is often characteristic of children of an earlier age. This can be observed best during the child's play. A method of bringing out primitive postural responses is carried out in the following manner:<sup>29</sup> The



child stands with the arms extended in front of him and his eyes closed. The examiner then rotates the child's head to one side. The primitive response to this test is to turn the body so that it is in line with the head. So long as the examiner continues to turn the head the child continues to turn on his longitudinal axis. This is normal for children from the time they are able to cooperate with the test until about 6 years of age. Thereafter the normal child will accept the turning of the head without rotating the body. After an initial displacement of the arms, he will correct the displacement.

The child with cerebral damage responds to this test like the younger child, rotating on his longitudinal axis as long as the head continues to be turned. A similar but exaggerated response, whirling, is obtained in the child with schizophrenia.

The brain-damaged child may show some dissociation of movements in walking and talking. In walking the customary swinging movements of the arms may be absent or irregular. Similarly, in the act of talking the normal smooth coordination between the act and respiration may be disturbed. The absence of appropriate facial expressions and associated gestures during speaking may also give an indication of organic brain disease.

Imperfect ocular convergence should be sought for. This is elicited by having the child try to converge on the finger placed on the end of his nose.

Occasionally abnormal muscle twitchings or tremors are observed.

Psychometric tests.<sup>28</sup> Children with organic brain disease have difficulty with tests which are dependent on spatial orientation, visual and auditory memory, and baragnostic sense (ability to distinguish weights). They are unable to copy a diamond (7-year-old test) and very young children are unable to copy a square. Memory for digits is poor, especially backwards. The children are unable to reproduce designs from memory and often fail to distinguish weights as well as one would expect from their general test performance. In reproducing designs from memory, a basic pattern suggestive of the original picture is generally made, but perseverative activity results in an almost endless repetition of the same primitive design.

Discrepancies between the performance on the Stanford-Binet test and on the Goodenough Draw-a-Man test are wide. A score of 2 years or more in the Goodenough test below that obtained in the Stanford-Binet is highly suggestive of organic brain disease. The ability to draw a man may, however, be unimpaired.

#### PSYCHOPATHOLOGY

It is not to be assumed that all of the symptoms observed in the brain-damaged child are organically determined. In good part the behavior is a result of the child's awareness of his inadequacies and his reaction to them. Bender<sup>28</sup> points out that, during the early months of life, the mother (or mother substitute) functions not only to give food, affection, and personal care to the child but she also gives him support in his motor activities. The infant is as much dependent on the mother for motor support as he is for food. In a brain-damaged child it may be necessary to supply this motor support for a much longer

period of time than normally, not only as far as locomotion is concerned but also in feeding, dressing, undressing, and even in speech.

Afflicted children tend to cling to the mother or a substitute and, as a result, they develop deep emotional attachments and dependency relationships. To a considerable extent excessive maternal care is actually a response to the child's real need. Depriving him of needed support may induce profound anxiety states. Thus the brain-damaged child may be retarded not only in his motor development but in his emotional development as well. The clinging and dependency made necessary by the motor defect have their counterparts in the emotional sphere.

The observations of Bender are based on a study of children with cerebellar dysfunction<sup>30</sup> which often exists in relatively pure form and is not complicated with other perceptual or impulse disorders. Similar conclusions to hers were reached by Schilder in his study of children with gross damage to the brain<sup>31</sup> and in his experience with adult obsessional problems.<sup>32</sup> He concluded that unsolved motor problems in early childhood may well be a factor leading to anxiety neurosis later on and may be connected with compulsive and obsessional neurosis.

One of the principal defects in the functioning of the brain-damaged child is an inability to integrate perceptions. Perception itself is not disturbed. The difficulty lies in synthesizing the perceptions into a logical whole. The child's dissatisfaction with his inability to make contact with his environment leads to increased attempts on his part to understand what goes on about him. This is expressed by hyperkinetic behavior, and the drive to touch, see, hear, feel, and finally to destroy every object which cannot otherwise be appreciated.

Anxiety is prominent in the brain-damaged child but it is generally concealed. It is of the diffuse, nonspecific type and often does not relate to real situations. Bender<sup>28</sup> explains the anxiety as the child's reaction to his own inadequacies. It is a factor intensifying his clinging behavior, his impulsiveness, and his overactivity.

#### DIAGNOSIS

A behavior disorder on the basis of cerebral damage must be differentiated from a disturbance due to exogenous causes, e.g., improper home environment, and schizophrenia. In favor of cerebral damage are:

1. History of an injurious episode usually in early life. (Gesell and Amatruda<sup>27</sup> have observed a group of infants who presented atypical behavior presumably on the basis of cerebral damage but in whom no evidence of abnormality in the birth or neonatal histories could be found.)
2. The symptom complex of hypermotility, impulsiveness, short attention span, rapid change of mood, variable memory, and poor performance in arithmetic.<sup>17</sup>
3. The absence of an emotionally traumatic home environment.
4. Changes in posturing and motility.
5. Changes in performance on psychometric tests.

The syndrome of schizophrenia in childhood is a complex one. It should be suspected when mental development which has been proceeding normally slows down or deteriorates. Mental development in the child with schizophrenia is likely to be irregular, the deviation affecting certain faculties, for example speech, more than others. Bradley<sup>33</sup> lists the symptoms of schizophrenia in children as follows: seclusiveness; irritability when seclusiveness is disturbed; day-dreaming and fantasies definitely in excess of what is usually seen in children of similar age and developmental status; bizarre behavior which consists of incongruous actions and activities such as repetitive, purposeless motions; unintelligible language and irrelevant expression of emotion; diminution of interests or failure to be attracted by objects and activities which one usually anticipates in children of similar age and intelligence; regressive personal interests or the voluntary selection of and participation in amusements and occupations which customarily intrigue children of younger age levels; sensitivity to comment and criticism (i.e., excessive emotional response to such personally directed opinions of others as praise, blame, etc.); and physical inactivity (i.e. conspicuously less gross motility than is commonly seen in other children of the same age and developmental status).

*Electroencephalogram:* Little in the way of diagnostic aid can be expected from the electroencephalogram. Although abnormal tracings are obtained in a high proportion of brain-damaged children, they are also often seen in children with simple behavior disorders.<sup>34</sup> There is nothing characteristic in the tracings of brain-damaged children. In a recent study by Levin,<sup>35</sup> children with post-encephalitic behavior disorders showed, for the most part, mild changes, principally of the slow wave type. A few showed severely abnormal tracings and occasional fast activity. Dees<sup>36</sup> observed electroencephalographic changes in a large number of children with asthma, which tended to become normal with control and improvement of the allergy.

*Prognosis:* The fact that a child's misbehavior is due to cerebral damage does not mean that the prognosis is necessarily hopeless or even bad. The outlook depends more on the extent of the cerebral injury and on the treatment than on the nature of the offending agent. The dominating drive in the brain-injured child, as in the well child, is toward normal maturation. This is a force capable of overcoming many obstacles.<sup>28</sup>

Preston<sup>13</sup> found the over-all prognosis in children with behavior disorders associated with anoxic damage to the brain to be good, especially if the diagnosis is made early and if proper treatment is instituted. In the group which she studied, once the parents and teachers came to understand that the child's misbehavior stemmed from a defect for which he was not responsible, much of the rejection was modified and greater tolerance was shown toward him. Gesell and Amatruda<sup>27</sup> have also observed a tendency toward improvement in children with minor cerebral injury.

*Treatment:* The child who misbehaves on the basis of cerebral damage needs, from the very start, an extra amount of maternal affection, attention, and support. The parents and teachers need to know that the misbehavior is

not the child's fault but that it stems from his defect. All along the line the child needs extra praise, encouragement and approval.

The advisability of nursery school attendance should be carefully weighed. The child should be allowed to attend only if he seems capable of giving a fair amount of attention and concentration. It may even be wise to postpone entrance into grade school.

Much can be done for these children prophylactically. Where there is reason to believe that a cerebral injury has been sustained, the child should be given extra support and affection before his symptom develops, even at the expense of setting up undesirably close emotional attachments and dependency relationships.

Benzedrine is a valuable therapeutic aid in some of these children. As an initial dose 5 mg. may be given daily once a day on rising to a 5-year-old child. The dose is increased rapidly until a therapeutic or toxic effect is obtained. Occasionally very large doses—up to 20 or 30 mg. a day—are tolerated.

#### SUMMARY

1. A disturbance in behavior may be the most prominent manifestation of cerebral damage of varying etiology in children.
2. The clinical syndrome is fairly characteristic.
3. Subtle neurologic changes and the performance on psychometric tests are diagnostic aids.
4. In general, the outlook for improvement in behavior and ultimate recovery is good.
5. Treatment consists of giving the child added support at home and in school in the form of extra affection, attention, approval, encouragement, and praise.

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# The Social Aspects of Medicine

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## HOW "FREE HEALTH" WORKS OUT\*

[Editor's Note: Last year the JOURNAL published several discussions of the British Medical Health Act which went into effect early in July, 1948. A number of reports have appeared recently discussing the working of the Act during its first six months. One of the most objective discussions appeared in the January 21 issue of the *U. S. News and World Report* and is reprinted with their kind permission.]

Boom in medical care in Britain shows what happens when the Government takes over all health services.

Some doctors are making more in Government service. Others find it costs them money. Specialists have most trouble.

But public likes it. Nearly everybody wants teeth fixed, tax-paid glasses, pills, a free checkup for the family.

IF BRITISH experience means anything, American doctors and the American public are due for surprises, when and if national health service is started in the United States.

The medical business, in light of British experience, then will enjoy an unprecedented boom. Dentists and opticians, in particular, will be swamped with customers. Income of many physicians, dentists, druggists, opticians, optometrists and others will grow, although work will be harder. Sick people often will find that they have to wait in line for hours to see a doctor, and that they must wait weeks or months to get into a hospital for a needed operation.

Socialized medicine is turning out to be popular in Britain. It is favored by most of the people and by many in the medical and dental professions. Lord Beaverbrook, who strongly opposed socialism for Britain, now says that "the national health scheme has been the greatest vote-winning success since Lloyd George introduced old-age pensions." But costs are high.

Britain is to spend the equivalent of \$1,300,000,000 for the national health plan in its first 12 months. There are only one third as many people in Britain as in the United States. A similar plan for U. S., if no frills were added and payments for medical service were no higher than in Britain, would cost around \$4,000,000,000 a year. With American standards, it could easily cost \$5,000,000,000, and opponents claim it would run as high as \$7,000,000,000. There is little prospect, however, that Congress will approve such a measure soon.

Doctors taking part in Britain's plan are paid the equivalent of about \$3.25 per patient per year. They receive their pay from the Government once every three months. Dentists are paid by the Government according to the services they render.

\*Reprinted from *U. S. News and World Report*, an independent weekly magazine on national and international affairs. Published at Washington. Copyright 1948, United States News Publishing Corporation.

Some of the doctors, such as those in the poorer districts of London, enjoy an increased income under this system. If they serve the maximum of 4,000 public patients, they have an income of at least \$13,000 a year, though they work harder and longer for that income.

But socialized medicine has hurt many other doctors whose patients were among the well-to-do. Under the rules, a doctor is supposed to be free to accept or reject patients, as he sees fit. But, in actual practice, he finds that he can't be as choosy about his patients as the regulations indicate. Besides, he is not free to charge what he wants, except where patients prefer to retain him on the old private basis.

A heart specialist, for example, whose income was above \$20,000 a year in the past, now is trying to split his efforts between public and private patients. But he finds he is losing his private patients. If his private patients continue to drift away, he may not be able to carry on a mixed practice for long, and may be forced into full-time public work. In any case, his income is reduced. And those who still are willing to pay well for his services discover that he is unable to give them the time and attention he once did.

The lure of free medical care and free dental service has caused more than 90 per cent of the people in Britain to enroll under the national health plan. In unprecedented numbers, they are besieging the doctors' and dentists' offices for advice and treatment.

Dentists especially are in demand as never before. For many years, visitors to Britain have commented on the poor condition of British teeth and the small number of dentists available. When dentistry became free, a stampede ensued. The dentists began working 16-hour days. Their fees piled up and the income of some dentists has run as high as \$40,000 or even \$50,000 a year. Recently, the British Government has ruled that dentists must cut their fees in two after their gross income exceeds \$19,000 annually.

Observers point out that the experience of British dentists might not be fully duplicated in the United States. The teeth of Americans have had somewhat better care than those of the British people, and the number of dentists per capita is greater in U.S. than in Britain. However, the British experience shows that, if free dental service were offered in U.S., a rush to the dentists' offices could be expected.

Many British doctors find life more exacting under socialized medicine. One, for example, reported that he was telephoned in the middle of the night by a man who had had a boil on his back for over a week and thought the doctor ought to know about it. Frequently, when a mother consults a doctor for herself, she takes along her smallest children and asks to have them examined, and also inquires about the care of older children in her family. This greatly increases the demands on physicians' time.

Free drugs and free health appliances are very popular, too. If a doctor approves, a patient is entitled to free eyeglasses, a free artificial leg, a free hearing aid, or even a free wig.

The optical business in Britain now is booming. Official estimates are that at least 90 per cent of the persons tested have been found to require glasses.

These are being provided at a rate of 7,500,000 pairs a year—nearly double the previous rate. But supply cannot keep up with demand, and a person entitled to glasses has to wait from one to three months before his order can be filled.

For many druggists, volume of business has doubled. Once a month, they report to the Government the number of free prescriptions supplied. The Government is trying to set an average price for a prescription to avoid a complex system in which each prescription, in each quantity, would be paid for separately. Pending the outcome of these negotiations, druggists are being advanced a flat sum equal to about 35 cents for each prescription filled.

People frequently find that they have to adjust themselves to the convenience of physicians and suppliers. After waiting in line in the doctor's office, the patient may find that the doctor shows little concern about his ailment. Or a person desperately ill at home may have trouble in persuading a doctor to call.

Delays are likely all along the line. Hearing aids have been supplied to only 5,000 of the estimated 150,000 persons in need of such assistance. Dental appointments often must be made weeks in advance.

Hospital facilities are short, too. Mothers are encouraged to have their babies at home, and hospital care is prescribed only in the event of necessity.

A small portion of hospital space is reserved for private, paying patients. For example, a person needing an operation for hernia can get that performed as a private service within a week. But, if he is a public patient and the operation is not urgent, he will have to wait, even up to several months.

One criticism is that a patient wishing the comfort of a private bed in a hospital and paying for it is not allowed to deduct from his bill the cost of a bed in the public ward.

Some people, who are getting better medical care than they previously could afford, welcome the benefits and do not complain about the delays. But the long waits are annoying to persons who were accustomed to prompt service in the past.

Apparently, many years will elapse before Britain has enough dentists, nurses, and hospitals to meet the demand for free health service. A similar situation could be expected in the U.S. if President Truman's health plan should be approved some day by Congress.

Over the long range, socialized medicine in Britain faces several hazards. The cost may prove greater than the public treasury can stand. The plan eventually may bog down under the weight of bureaucracy. If rewards are too meager, fewer young people may be attracted into the medical profession. Opponents of the plan predict that the end result will be a lower standard of medical care.

What the doctors in Britain, as in U.S., fear most is that, sooner or later, they will be forced into clinics to practice medicine, Russian style, at fixed salaries. It is too soon to predict the outcome of Britain's national health scheme. But the popularity of the scheme in its first six months seems to assure that it will get a long trial.



## Comments on Current Literature

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### IRRADIATION OF LYMPHOID TISSUE IN DISEASES OF THE UPPER RESPIRATORY TRACT

**D**ETAILED knowledge concerning the anatomy and physiology of the upper respiratory tract has emphasized the important part played by this region in maintaining the health and well-being of the individual: in the regulation of the temperature and humidity of the inspired air, the activity of the ciliated epithelium, the role of lymphoid tissue as a first line of defense against upper respiratory infection, in the production of antibodies and the process of immunity.

Proctor, Polvogt, and Crowe<sup>1</sup> have reported recently the results of an extensive study of lymphoid tissue in relation to diseases of the upper respiratory tract and the therapeutic irradiation of lymphoid tissue.

These authors point out that the real vulnerable point in the upper respiratory tract is the nasopharynx, since all air-borne organisms gaining access to the interior of the body pass through the nasopharynx and over the adenoids. The anatomical characteristics of tonsillar and adenoid tissue where crypts may be deep and intricate predispose to the retention of viable bacteria and the setting up of disease processes. Since there is no simple way to prevent air-borne organisms the nasopharynx may be the starting point for virus or pyogenic upper air passage infections and their complications.

In an effort to overcome these hazards to some extent, surgical removal of tonsillar and adenoid tissue has been practiced widely. However, while surgical removal has been beneficial in many instances, statistical studies indicate that such removal leaves much to be desired with respect to the subsequent incidence and severity of upper respiratory infection. Lymphoid tissue not only regenerates readily, but also is so much an integral part of the mucous membrane of the posterior and lateral walls of the pharynx and nasopharynx that all of it cannot be removed surgically.

In a discussion of the important protective mechanisms in the upper air passages, Proctor, Polvogt, and Crowe state that although lymphoid tissue is most abundant in the midline of the nasopharynx and in the fossa of Rosenmüller, "after surgical removal of adenoids in children nodules of this tissue often appear in and around the pharyngeal orifice of the eustachian tubes, in the choanae near the posterior end of the middle turbinates, and on the posterior and lateral surfaces of the vomer. These facts concerning the distribution of lymphoid tissue in the nasopharynx and posterior part of the nose are important for a clear understanding of recurring colds, of certain types of impaired hearing, attacks of suppurative otitis media and mastoiditis, ethmoiditis and chronic post-nasal discharge."

These authors advocate the use of irradiation by radon or radium applicator for the removal of recurrent lymphoid tissue following adenoidectomy and particularly for displaced nodules of lymphoid tissue in and around the pharyngeal orifice of the eustachian tubes that often lead to impaired hearing. They have employed this type of therapy in selected cases with increasing confidence and satisfaction for some twenty years. At first, irradiation therapy was used by them almost exclusively for the treatment of certain types of impaired hearing. However, as free beds became increasingly more difficult to obtain over the

years, they began to use this type of treatment for complaints which formerly were thought to justify operative removal of tonsils and adenoids. In selected cases they have found the procedure an invaluable therapeutic measure.

Details of the therapy are given and at the present time the Monel Metal Radium Applicator seems to be the instrument of choice. The authors state that well over 1,000 applicators are now in use in this country and that to their knowledge no complications arising from the procedure itself have been reported. Dosage is controlled carefully and undesirable secondary radiations are screened out.

During the studies carried out over the past five years, follow-up on many patients has been possible, especially among the group of children treated at the Hagerstown Clinic where more than 1,000 patients have been seen during this five-year period. A statistical study has been made on a group of 400. These children were treated with radium because of recurrent respiratory or ear infections, hearing impairment or bronchial asthma, and the authors feel that the treatment has been of major assistance in avoiding some of the most common serious problems of childhood such as ear infections and hearing impairment. In most of the 400 children included in this statistical study, the last examination was performed about one year following the completion of therapy.

More than 83 per cent of all children seen in this clinic because of hearing impairment had histories of recurrent otitis and upper respiratory infections thought to account for the impairment. The number of children whose hearing improved following irradiation amounts to nearly one-half of the group with impaired hearing before treatment. In a number it was possible to arrest progressive impairment and it is hoped that in some of these at least there will be improvement of hearing. Of the 400 children in this group, seventy-one underwent surgical removal of lymphoid tissue during the period of observation. In 191 patients lymphoid tissue had been removed surgically prior to their first clinic visit.

With respect to the treatment of children with bronchial asthma, Proctor, Polvogt, and Crowe state that the effects of irradiation have been difficult to evaluate. In a number of instances where the asthma was on an infectious basis, improvement in the asthmatic condition was dramatic. Careful consideration of all factors led them to conclude, however, that irradiation of the nasopharynx in bronchial asthma must be considered a helpful auxiliary to other forms of treatment, since infected adenoid tissue may be merely an accompaniment. Of forty-one children with bronchial asthma treated by irradiation of the nasopharynx, the average follow-up period has been thirty-five months. The majority of these children had desensitization therapy or other standard measures of treatment.

Clinical observation of the results of a treatment technique employed over a period of twenty-four years deserves attention and consideration. The results reported by the authors support amply their modest claim that while "irradiation of the naso-pharynx with a radium applicator is no panacea ----- in selected cases it is an invaluable therapeutic measure."

RUSSELL J. BLATTNER.

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## News and Notes

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Dr. Abraham M. Litvak of Brooklyn, N. Y., died Jan. 30, 1949. He was chief of the pediatric service at Beth-El Hospital and associated pediatrician to the Jewish Hospital.

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The International and Fourth American Congress on Obstetrics and Gynecology will be held in New York City at the Hotel Statler, May 14-19, 1949. Dr. Fred L. Adair of Chicago is Chairman.

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A postgraduate course in pediatrics will be given by the Department of Pediatrics, University of Arkansas, Little Rock, on March 11 and 12, 1949. Guest speakers will be Dr. James G. Hughes of Memphis, and Dr. Myron E. Wegman of New Orleans.

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The 45th annual conference of the State Department of Health and State Health Officers Association of New York will be held at Lake Placid June 20 to 23. The Association of School Physicians will hold its annual meeting on the opening day.

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The officers of the Rocky Mountain Pediatric Society for 1949 are Dr. Wm. D. Rothwell, Jr., President; Dr. Mariana Gardner, Vice-President; and Dr. Edwin T. Williams, Secretary-Treasurer. All are from Denver.

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A nine months' postgraduate course in pediatrics will be given at the Washington University School of Medicine beginning Sept. 12, 1949. Detailed information may be obtained from Dr. Merl J. Carson, Assistant Dean, Washington University School of Medicine, Euclid Avenue and Kingshighway, St. Louis 10, Mo.

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The national report on the findings of the two- and one-half-year study of child health services is being published in two volumes by the Commonwealth Fund of New York. This publication will be marked by a dinner on April 2 in New York City. A nationally known layman and an outstanding authority in medicine and public health are being invited as guest speakers.

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The International Congress on Rheumatic Diseases will be held in New York City from May 30 to June 3, 1949. In addition to papers by prominent American physicians, some 150 physicians from foreign countries are expected to attend, among them Lord Horder of London who will discuss rheumatism as a national problem.

## Book Reviews

**The Psychological Origin and Treatment of Enuresis.** S. Smith, Ph.D., Seattle, Wash., 1947, U. of Washington Press, 70 pages. Price, \$1.75.

Dr. Smith's monograph is intended as a guide for the parents of children with enuresis. There is little in the book which will be new to the physician. Unfortunately, most parents as well will derive little benefit from the book. The psychological viewpoints presented are vague generalities which will serve only to confuse and frustrate parents who are hopefully seeking aid. Considerable space is devoted to a discussion, on the whole favorable, of "conditioning" methods of treatment such as the ringing of a bell or the release of a stream of cold water or air when the child wets. These methods have not found wide acceptance among physicians and their value is doubtful.

H. B.

**Premature Infants.** Ethel C. Dunham, M.D., Washington, D. C., 1948, Government Printing Office, 401 pages. Price \$1.25. (Superintendent of Documents, Washington, 25.)

This is a very valuable book. The author, who has been interested for many years in the problems of prematurity, has carefully compiled and edited from a bibliography of over five hundred references a complete text of our present-day knowledge of the premature infant. The first section has to do with general considerations as the causes and prevention of prematurity, the growth and development, and the prognosis of the premature infant. Part two takes up clinical considerations as the physical care and environment, the feeding and nutritional problems, and finally the question of diseases. It is a reference book that should be on the shelf of every pediatrician's library as in it will be found the answers to most of the problems and questions that arise in regard to the premature infant. The Children's Bureau is to be congratulated in sponsoring the text and making it available to physicians.

**Handbook of Pediatric Medical Emergencies.** Adolph G. DeSanctis, M.D., New York, 1948, Privately Printed. Department of Pediatrics, New York Post-Graduate Medical School and Hospital. Price \$2.00.

This is a very useful booklet of about ninety pages compiled by members of the pediatric staff of the New York Post-Graduate Hospital. The material has been accumulated over a period of years as a guide for residents and postgraduate students. The first section considers neurological emergencies such as coma and convulsions due to various causes, and their treatment. This is followed by emergency conditions of the cardiac, respiratory, gastrointestinal, and genitourinary systems. A most important section deals with various poisons and their treatment. A final section discusses miscellaneous emergencies as burns, hemorrhage, bites, etc. It does not pretend to be a text but fulfills its purpose of making information quickly and readily available as to how to handle pediatric medical emergencies. The treatment outlined under the various emergencies is sound and in keeping with recent medical progress. It is a booklet that could well be placed in the admitting room of every hospital. It may be obtained from the Secretary of the Pediatric Department, University Hospital, 303 East 20th Street, New York 3, N. Y.

**EMIC. A Study of Administrative Experience.** Nathan Sinai, Dr.P.H., and O. W. Anderson, Ph.D., Ann Arbor, 1948, School of Public Health, University of Michigan, 181 pages with 42 pages of appendix.

This is the report of a study of the administration of the EMIC program made by Dr. Sinai and his associates in 1943, financed by the New York and Marshall Field Foundations. The method of the Study was an analysis of the material and records in the Children's

Bureau and a field study in eight states from New York to California. Although the authors state "primary emphasis" was upon the field work, the report is chiefly based on the Washington end. It is purely a study of administration and does not concern itself with the more important problems of the quality of services rendered, except as an administration problem, nor the question as to whether a universally federal program is needed. The authors trace the constantly changing regulations and directions of an administrative nature issued by the Children's Bureau to meet the problems which developed as the program expanded and the difficulties which arose in adjusting the federal-state relationships. The problems of payment for service by physicians and hospital is discussed, including the unsuccessful attempt to establish geographic differentials. The authors are not so successful in their history of the program as so much has been omitted. That there was need for federal aid in a number of areas in the country as a result of situations created by the war is beyond question, as local services could not possibly meet the overwhelming demands for medical service thrust upon them. That there was need for a national program of federal payment for maternal and infant care is quite another matter. This report of EMIC considers it only as an administrative problem. If administrative experience in a national health program was the chief benefit from the program, the cost of over \$130,000,000 seems rather high to say the least.

**1948 Facts About Nursing.** American Nurses Association, 1790 Broadway, New York, 106 pages. Price 35 cents.

This report of a survey of nursing contains a wealth of statistics regarding the nursing profession. There are today some 435,000 registered nurses but only about two-thirds are active. Tables of nurse distribution and student enrollment are among the many interesting subjects included.

**Your Child or Mine.** The Story of the Cerebral-Palsied Child. Mary L. H. Burton in collaboration with S. H. Jennings, New York, 1949, Coward-McCann, Inc., 64 pages. Price \$1.25.

A small book containing the stories of six children with cerebral palsy of different types. It is not a medical text, but one intended to point out in a nontechnical way to the parents of children with cerebral palsy what can and cannot be done for them, and some of the psychologic and behavior problems which develop as a result of the handicap.

**Baby Book.** New York State Department of Health, 1948, 50 pages.

An excellent short book on infant care prepared by the Bureau of Maternal Child Care. About two-thirds of the text is concerned with parental attitudes in keeping with modern thought on infant care. Part II gives specific instructions as to details. An attractive, well-edited, and sound short book on infant care.

## Editor's Column

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### THE PREVENTION OF DENTAL CARIES

PEDIATRICIANS have been questioned frequently the past few years about the topical application of fluorine to prevent dental caries. The reply has usually been that it is still in the experimental stage but that its value is seemingly being established by carefully controlled studies. Recently another method of topical application received widespread lay publicity which has made the entire matter quite confusing. After discussing the subject with several dentists, Dr. Virgil Loeb, a well-known stomatologist, kindly consented to put the gist of our discussion into letter form for publication in the JOURNAL. It is, we feel, a sane attitude which will aid the pediatrician in giving sound advice to parents.

January 17, 1949.

Dear Dr. Veeder:

Because the pediatrician is called upon so often to advise parents relative to the prevention of dental decay in children, and because the subject during the past few months has been given wide and, at times, confusing publicity in the press and in articles in magazines, I am very happy to tell you what I believe to be the present opinion of most dentists regarding the subject.

As you know, a great deal of scientific research has been undertaken on the cause of dental caries, and while much has been learned, investigators are still not in agreement. Undoubtedly there are both local and systemic factors which may be responsible, either singly or in conjunction with one another. Though the etiology is still undetermined, several methods to control and reduce dental decay have been suggested. The one which has been most broadly publicized during the past few months is the use of sodium fluoride. Research carried out by very able men in the U. S. Public Health Service and elsewhere on an organized basis has established the fact that this agent, when properly used, reduces the incidence of decay by from forty to fifty per cent. The exact mechanism through which fluorine produces a lowered caries rate is not known, but enough statistical evidence has been accumulated during the past five or six years to warrant the statement that it has great potential value in controlling dental caries and, when used properly by a dentist, it can do no harm. It must be noted that in connection with the fluorine treatment, regular visits to the dentist at from three- to four-month intervals are advisable, and that proper home care and proper diet are indispensable.

I believe it can be said that no single method of caries control has received such favorable response from the dental profession as has the fluorine therapy. Additional support has been given by editorial and other comments in the *Journal of the American Dental Association*, the official journal of the dental profession.

The general public was beginning to be aware of and take comfort from the sodium fluoride therapy when, on January 8, an article appeared in *Collier's*

magazine, describing the impregnation theory of Dr. Bernhard Gottlieb and ascribing ninety per cent favorable results to the use of his treatment. The claims of such a "miracle" medicine have naturally enough confused the public as well as many physicians and dentists, and it is very important that the results described be carefully checked. According to the *Collier's* article, the treatment "has been perfected and proved in the last few months," but there appears scant clinical evidence to support the claims. Physicians and dentists should await the results of much more investigative work before suggesting this impregnation method.

I believe that at the present time the dental profession prefers to advise and use the fluorine therapy rather than the more complicated therapy suggested by Dr. Gottlieb, principally because the former has been investigated for several years and the results of its use in thousands of patients are available. There is, as yet, inadequate clinical evidence to prove the claims of Dr. Gottlieb.

I trust this analysis may be of value to you.

Sincerely yours,  
(signed) VIRGIL LOEB, M.D., D.D.S.

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### THE BRITISH MEDICAL HEALTH SERVICE

A LITTLE over six months have passed since July 5, 1948, when the British national health service went into effect. Reports vary somewhat but all are agreed it has cost much more than the original estimates. Glasses and dental services are way beyond expectations. Proponents of the plan argue that this shows the previous unmet needs of the British people, while opponents point to it as the grasping for something free. It was, of course, obvious from the start that the plan will have to be modified in the light of experience. A few weeks ago at a private dinner, a very high British official, who was the guest, was questioned as to the service and how it was working out. His reply was that it would take four or five years to really judge the value and success of the experiment, which was about as sound a judgment as we have heard. Most of the reports that have been coming back in recent weeks have seemed to us somewhat biased according to the attitude of the writer toward socialization as a political philosophy. The best report we have seen appeared in the January 21 issue of the *U. S. News and World Report*, which points out some of the problems that have developed, and which we have reprinted in the "Social Aspects of Medicine" column on page 383. Another brief account that we found of interest appeared in the January 15 issue of *The New Yorker* in the "Letter From London" by Mollie Panter-Downes. She makes one comment we have not seen elsewhere to the effect that some consider that "the Minister of Health, who is also responsible for housing, has put the cart before the horse. . . . The magnificent new machine of universal medical care can only, after all, do its best to patch up the effects of the appalling overcrowding and medieval discomfort in which thousands of displaced Londoners are still existing."

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## Original Communications

### THE EFFECT OF MILK SUPPLEMENTS ON THE GROWTH OF CHILDREN WITH NUTRITIVE FAILURE

#### THE WETZEL GRID FINDINGS

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FROM the moment of conception to the attainment of physical maturity, the growth of a person is characterized by an increase in size and an increase in cell complexity. Under optimum conditions the growth process is distinguished by a high degree of orderliness and stability. Growth may be thought of as the summation of the functions of a number of fundamental biochemical systems, any of which may be easily affected by a large variety of exogenous and endogenous factors. Prominent among these factors is a diet deficient in essential nutrients.

The effects of chronic malnutrition on the growth progress of children born to parents with long-standing nutritive failure in a region of endemic nutritional deficiency diseases have been studied at the Nutrition Clinic of the Hillman Hospital, Birmingham, Ala., since 1936. It has been observed and reported that, in general, the growth progress of such children is irregular, unstable, and retarded.<sup>1, 2</sup> Physically, the children are somewhat smaller and leaner than adequately nourished children of the same age group and racial stock.<sup>1</sup> Although specific nutritional deficiency lesions are seldom seen in infancy in children with chronic nutritive failure, they frequently appear early in childhood and show a pronounced tendency to recur in the late spring and summer when the incidence of retarded growth in this group is most common.<sup>3, 4, 5</sup>

Although the health of a child and his status as an adult cannot be measured in terms of size alone, prolonged failure to grow is extremely important, as every child must liquidate his growth debt by the time the epiphyses and diaphyses of the major long bones have fused; otherwise, he can never attain the maximum physical development dictated by his own growth pattern. In 1945, a special three-year study was initiated to determine the effect of the daily supplementation of a known amount of either whole or nonfat dried milk on the growth progress of a selected group of children with chronic nutritive failure. Three different methods, namely, analyses of roentgenograms of the hand, wrist, and forearm, photographs in the nude, and

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the Wetzel Grid were used singly and in conjunction, to measure the changes in growth which occurred in each child during the period of investigation.<sup>2</sup> The present report is confined to the Wetzel Grid findings.

#### MATERIALS AND METHODS

*Selection of Patients.*—The eighty-two subjects included in this study were selected from more than 300 children who were patients of the Nutrition Clinic. The preliminary selection was made on the basis of: (a) history or evidence of nutritive failure in the child, parents, or older siblings; (b) chronological age; (c) freedom from contagious or infectious disease and allergy to cows milk; and (d) accessibility of the home and the cooperative attitude of the parents.

After considering the roentgenographic and height-weight data of each of the children who met the preliminary requirements, forty-one pairs of children were chosen for this investigation. The forty-one pairs included twenty-three pairs of girls and eighteen pairs of boys, ranging in age from 4 to 15 years. All of the subjects were white, of Anglo-Saxon extraction, and, for the most part, natives of north-central Alabama. The criteria for the pairings were: (a) sex; (b) comparative roentgenograms of the left hand, wrist, and forearm; (c) general body type; and (d) the apparent prevailing phase of growth.

*Method of Study.*—The period of study comprised three different phases: namely, (a) a premilk phase of several years' duration in which the data used in the selection of some of the children were collected and the methods subsequently used to measure growth progress introduced, tested and, evaluated; (b) a milk phase, which began in April, 1945, and extended for twenty months (during this time one child in each pair was given a supplement of the equivalent of one quart of milk each day, six days a week); and (c) a postmilk phase, which began immediately after the discontinuation of the milk supplement and extended for twelve months. The findings reported in this paper cover only the milk and postmilk phases, the two periods in which all of the selected children were subjected to arbitrarily fixed standard procedures based on the experience obtained during the premilk phase.

The supplement for one child in each pair consisted of either 3 ounces of nonfat milk powder or  $4\frac{1}{4}$  ounces of whole milk powder. The additional  $1\frac{1}{4}$  ounces of whole milk solids were given in order to keep the protein content of the two types of supplement approximately the same. Twenty-two children (nine boys and thirteen girls) received the nonfat milk, while nineteen (nine boys and ten girls) received the whole milk. The milk powder was mixed with water by an electric churn under aseptic conditions, and in most instances brought up to one pint volume (approximately 500 c.c.) by clinic personnel under the direction of Miss Jean Grant and Miss Catherine Sims. To facilitate intake, the final volume in some cases consisted of one-half pint (approximately 250 c.c.), but in no instance was the amount of milk

NUTRIENTS SUPPLIED BY DIET OF CHILD\*  
WITHOUT AND WITH SUPPLEMENT OF DRY NONFAT MILK  
CONTRASTED TO RECOMMENDED ALLOWANCES OF NUTRIENTS\*\*

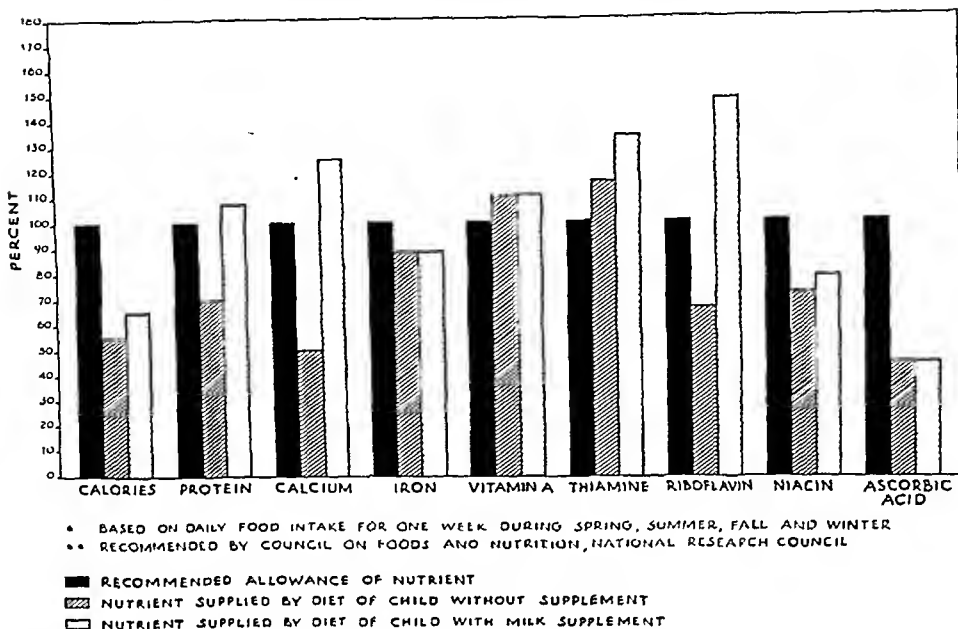


Fig. 1.—A representative diet of a child in the test group with and without the nonfat milk supplement.

NUTRIENTS SUPPLIED BY DIET OF CHILD\*  
WITHOUT AND WITH SUPPLEMENT OF DRY WHOLE MILK  
CONTRASTED TO RECOMMENDED ALLOWANCES OF NUTRIENTS\*\*

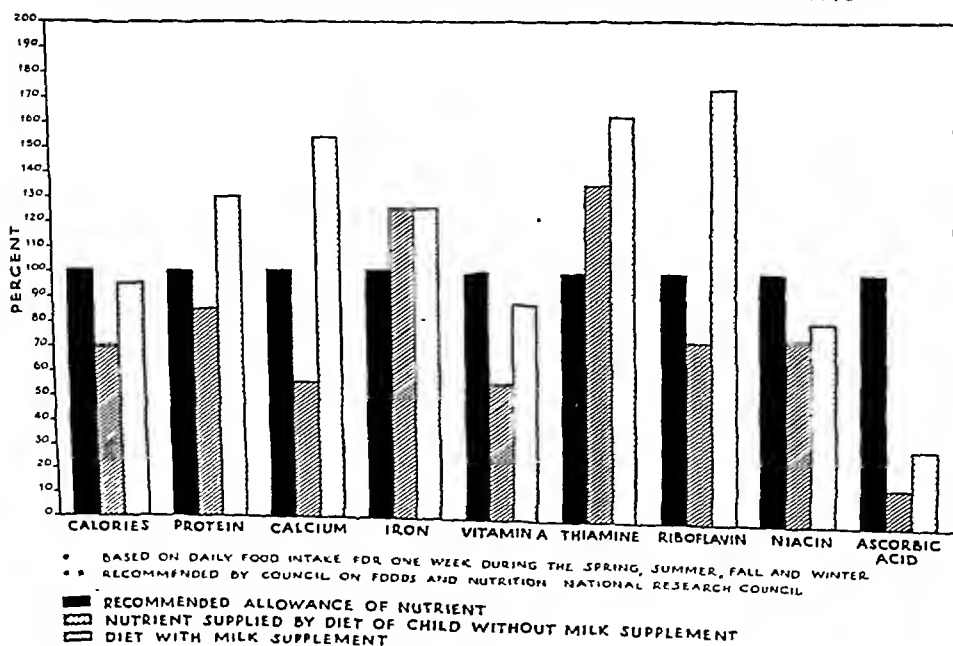


Fig. 2.—A representative diet of a child in the test group with and without the whole milk supplement.

solids given per day reduced. The suspended milk was placed in a refrigerator overnight and personally given to the children the next day by Miss Martha Hutchinson, Mrs. Nelwyn Dill, Miss Catherine Sims, Miss Verna Lee Moore, Mrs. Merle Babb, Mrs. Martha Nez, Miss Jerome Kennedy, Miss Jo Gilley, and Mrs. Mabel Morey, social service workers on the staff of the Nutrition Clinic. Each worker was assigned a number of children and had the responsibility of getting the milk to these children and seeing that the supplement was ingested by each child. When the supplement was refused in whole or in part at any time for any reason, it was returned to the clinic and the amount refused was noted on a record kept for each child. The effect of the milk supplement on the nutritive value of representative diets of two of the children included in the study are shown in Figs. 1 and 2.

No attempt was made to alter the habits of the children in any way other than by giving them the milk as a supplement to their daily dietaries. Any voluntary changes in the living conditions, habits, or dietaries of any of the children which occurred during either the milk or postmilk phase were noted and reported by the social service workers. In order to estimate the effect of the supplement or lack of it on the growth progress of each child, the following principles of therapy were applied: (a) symptomatic treatment and treatment for coexisting diseases other than nutritional deficiency diseases were given when indicated; (b) no nutritional therapy or dietary supplements other than milk were prescribed or added; and (c) conditions causing excessive requirements for the various nutrients were analyzed wherever possible.

Each child was brought to the clinic for examination for evidence of nutritive failure at least once every two months. A complete physical examination was made on each child once each year by Dr. Esther Gross. The children were weighed and measured at each of these examinations. Height was obtained by use of the Baldwin Paper Measuring Scale.<sup>6</sup> The shoes were removed and each child's height was taken in the standing position with the feet together and the heels, buttocks, shoulders, and head touching the scale. Weight was obtained with a Continental scale, the children being required to remove their shoes and outer clothing before being weighed.

The height-weight data for each child were plotted on individual Wetzel Grids.<sup>7</sup> Recently the originator of the Wetzel Grid published a treatise in which may be found many of the technical details for evaluating physical fitness in terms of physique (body build), developmental level, and basal metabolism.<sup>8</sup> Only those salient features of the Grid technique which formed the basis for the analysis of the Grid data included in this study are presented in the following paragraph.

According to the interpretation of the authors, in the Grid technique the quality of a child's growth is determined from an analysis of the direction and speed of his development.<sup>8</sup> The direction of development is denoted by the child's position in the channel system as plotted from successive points and compared to the direction of the channel system itself. The speed of

development is indicated by the position of the child in the auxodrome panel, plotted from successive points and related to the standard age schedules of development. Growth to be acceptable in quality, should not deviate beyond stated limits of tolerance either in direction or speed from the pattern set by the channel system or standard auxodromes. The limits of tolerance are a shift of one-half channel per ten levels of advancement and a deviation of not more than two to three levels per year from the expected schedule.<sup>9</sup> By the Grid technique, therefore, the objective signs of failing growth consist of: (a) developmental lag or the failure of the child to keep up with his expected age schedule of development, and (b) loss of physique characterized by a shift in the channel curve to the lower outer border of the channel system.<sup>10</sup>

#### OBSERVATIONS

For ease of presentation, the findings derived from the Wetzel Grid data for each child during both the milk and postmilk phases of the study are listed under five aspects of growth progress, each of which was evaluated by the Grid technique. These include: (a) direction of development, (b) speed of development, (c) rate of development,<sup>\*</sup> (d) quality of growth, and (e) incidence of episodes of growth failure.

#### THE EFFECT OF THE MILK SUPPLEMENTS ON THE DIRECTION OF DEVELOPMENT (WETZEL)

*The Milk Period.*—The changes in the direction of development of the test and control groups of children during the twenty-month period in which they received the milk supplements are shown in Figs. 3 and 4. It will be noted that in fourteen (34 per cent) of the children who received the milk supplements, the direction of development improved, while in nine (22 per cent) there was no change, and eighteen (44 per cent) drifted to the right and down, indicating a loss of physique. In the same period the physique improved in six (15 per cent) of the children in the control group, there was no change in eleven (27 per cent), and there was a loss of status in twenty-four (59 per cent). A summary of these findings is shown in Table I. Improvement in direction of development during this period was most frequent among the girls receiving the nonfat milk, followed in incidence by the boys receiving the whole milk, the girls receiving the whole milk, the girls in the control group, the boys receiving the nonfat milk, and the boys in the control group.

*The Postmilk Period.*—The changes in the direction of development which occurred among both groups of children during the twelve-month postsupplementation period are included in Figs. 3 and 4. In ten (24 per cent) of the children in the test group the physique rating improved, in sixteen (39 per

<sup>\*</sup>The rate of the 67 per cent auxodrome (i.e., the speed of progress called for by that auxodrome at successive ages) is approximately one level line per month throughout its entire range. The rate of every other auxodrome is also approximately one level per month over the same range. The rate of development is, therefore, independent of auxodrome from 5 years of age and up and is approximately the same for children on any and all auxodromes.<sup>11</sup>

# PHYSIQUE CHANNEL CHANGES IN 41 CHILDREN WHO RECEIVED THE MILK SUPPLEMENT (MILK AND POST MILK PERIODS)

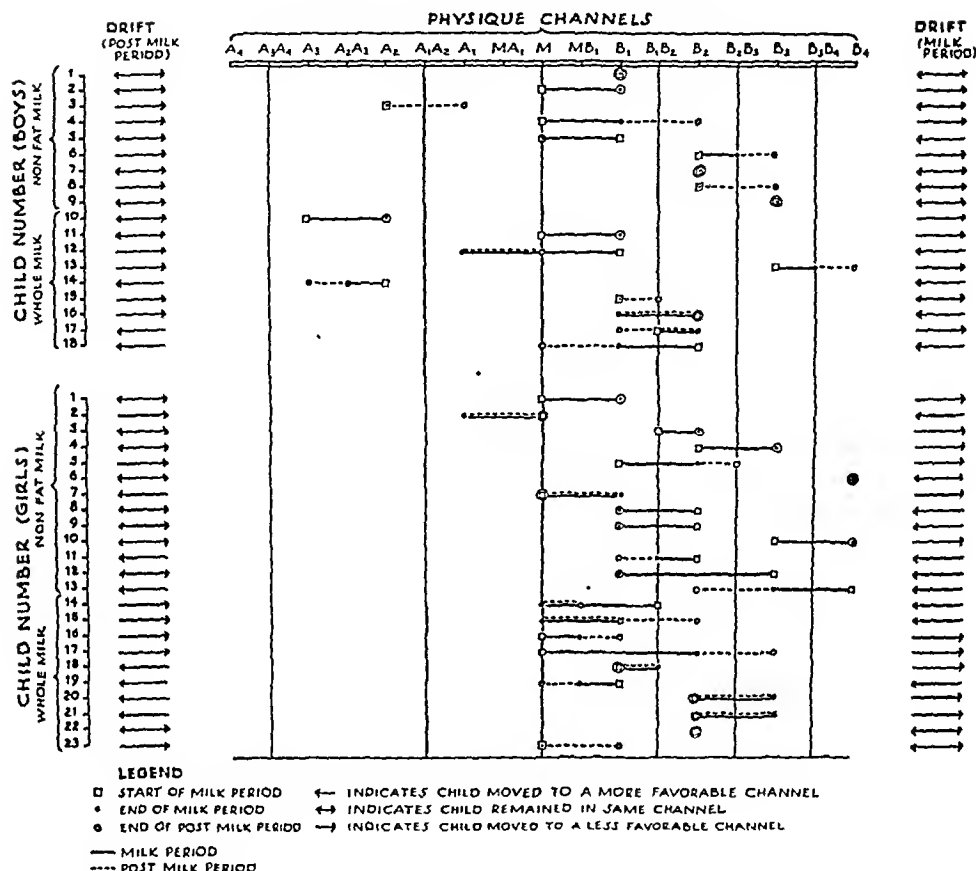


Fig. 3.—The changes in direction of development in the children receiving the milk supplements during the milk and postmilk periods.

cent) it did not change, whereas fifteen (37 per cent) moved into less favorable channels. The corresponding values for the children in the control group were seven (17.5 per cent), seventeen (42.5 per cent), and sixteen (40 per cent). One of the children in the control group did not return for examination during this phase, and is, therefore, not included in this tabulation. The findings of the postmilk period are summarized in Table II. The most extensive improvement in direction of development during this period occurred in the girls who had received the whole milk, followed in frequency by the boys who had received the whole milk, the girls who had received the nonfat milk, the girls in the control group, the boys in the control group, and the boys who had received the nonfat milk.

# PHYSIQUE CHANNEL CHANGES IN 41 CHILDREN IN THE CONTROL GROUP (MILK AND POST MILK PERIODS)

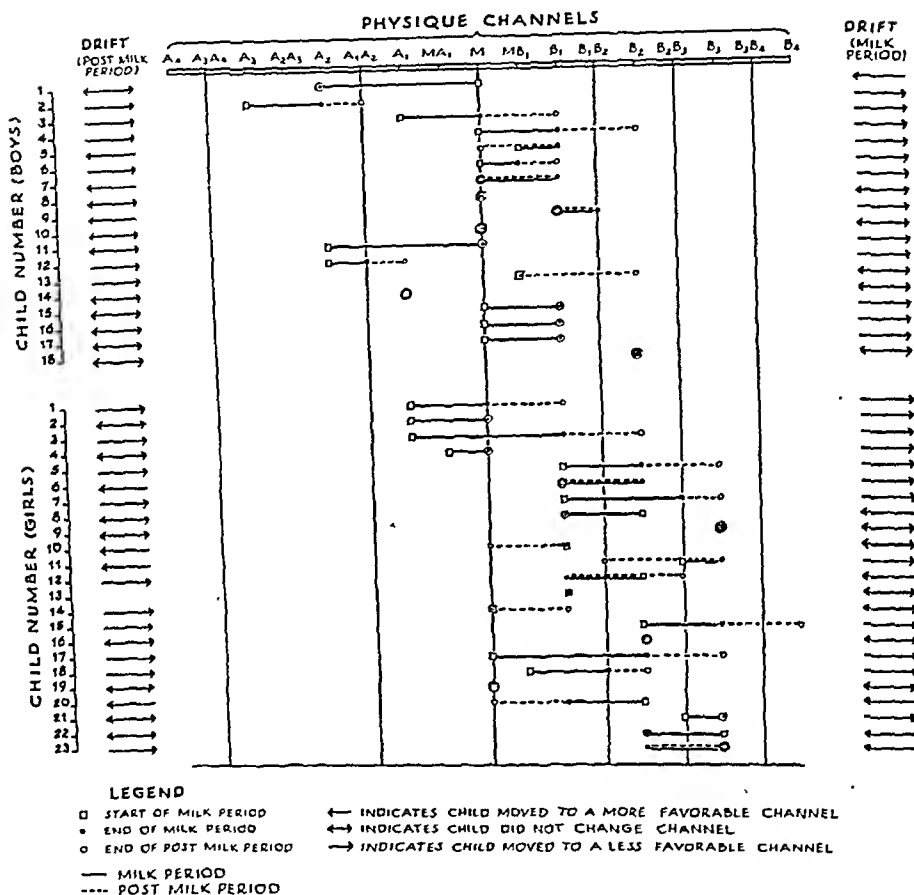


Fig. 4.—The changes in direction of development in the children in the control group during the milk and postmilk periods.

Five of the fourteen children in the test group who had bettered their direction of development during the milk period continued to improve in this respect throughout the postmilk phase of the study. Direction was maintained in four of the fourteen children, while in five there was a loss of status. Of the six children in the control group in whom improvement in the direction of development occurred during the supplementation period, one continued to improve, three maintained their direction, and two moved to less favorable channels in the postmilk period (Table III).

TABLE I. CHANGES IN GROWTH AS DETERMINED FROM THE WETZEL GRID IN FORTY ONE TEST AND FORTY ONE CONTROL CHILDREN DURING THE TWENTY MONTH PERIOD OF MILK SUPPLEMENTATION

TYPE OF CHANGE	TFST CASES										CONTROL CASES									
	WHOLE MILK					NONFAT MILK					BOYS					GIRLS				
	BOYS		GIRLS		TOTAL	BOYS		GIRLS		TOTAL	BOYS		GIRLS		TOTAL	BOYS		GIRLS		TOTAL
	NO.	%	NO.	%		NO.	%	NO.	%		NO.	%	NO.	%		NO.	%	NO.	%	
Channel Changes: (Direction of Development)																				
More favorable position	4	44.4	3	30.0	1	11.1	6	46.2	14	34.1	1	5.5	5	21.7	6	14.6				
Position unchanged	1	11.1	2	20.0	5	55.5	1	7.7	9	22.0	5	27.8	6	26.1	11	26.8				
Less favorable position	4	44.4	5	50.0	3	33.3	6	46.2	18	43.9	12	66.7	12	52.2	24	58.5				
Changes in Auxodrome: (Speed of Development)																				
Faster auxodrome	8	88.9	4	40.0	2	27.2	8	61.6	22	53.6	1	5.5	2	8.7	3	7.3				
Auxodrome unchanged	0	00.0	1	10.0	1	11.1	0	00.0	2	4.9	1	5.5	3	13.0	4	9.8				
Slower auxodrome	1	11.1	5	50.0	6	66.6	5	38.4	17	41.5	16	88.9	18	78.3	34	82.9				
Changes in Levels per Month: (Rate of Development)																				
More than one level per month	8	88.9	8	80.0	5	55.5	9	69.2	30	73.2	8	44.4	8	34.8	16	39.0				
Exactly one level per month	1	11.1	0	00.0	0	00.0	1	7.7	2	4.9	0	00.0	0	00.0	0	00.0				
Less than one level per month	0	00.0	2	20.0	4	44.4	3	23.1	9	22.0	10	55.5	15	65.2	25	61.0				
Changes in Growth Quality: (Speed and Direction of Development)																				
More favorable channel; faster schedule	4	44.4	3	30.0	0	00.0	4	30.8	11	26.8	0	00.0	0	00.0	0	00.0				
More favorable channel; schedule unchanged	0		0		0		0		0		0		1	8.7	1	7.3				
Channel unchanged; faster schedule	1	11.1	2	20.0	1	11.1	1	7.7	5	12.2	1	5.6	1		2					
Channel unchanged; schedule unchanged	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	1	5.6	0	00.0	1	2.4				
More favorable channel; slower schedule	0		0		1	22.2	2	46.2	3	26.8	1	5.6	4	21.7	5	14.6				
Less favorable channel; faster schedule	3		0		1	4	4		8		0		1		1					
Channel unchanged; slower schedule	0	00.0	0	00.0	4	55.5	0	00.0	4	12.2	3	16.7	5	30.4	8	24.4				
Less favorable channel; schedule unchanged	0		0		1		0		1		0		2		2					
Less favorable channel; slower schedule	1	11.1	5	50.0	1	11.1	2	15.4	9	21.9	12	66.7	9	39.1	21	51.2				
Number of Instances of Growth Failure: (Simultaneous Loss in Speed and Direction of Development)																				
0	5	55.5	3	30.0	1	11.1	2	15.4	11	26.8	3	16.7	5	21.7	8	19.5				
1	2	22.2	5	50.0	2	22.2	5	38.5	14	34.1	8	44.4	5	21.7	13	31.7				
2	1	11.1	2	20.0	3	33.3	5	38.5	11	26.8	5	27.8	13	56.5	18	43.9				
3	1	11.1	0	00.0	2	22.2	1	7.7	4	9.8	2	11.1	0	00.0	2	4.9				
4	0	00.0	0	00.0	1	11.1	0	00.0	1	2.4	0	00.0	0	00.0	0	00.0				

TYPE OF CHANGE															
NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%				
Channel Changes: (Direction of Development)															
3	33.3	4	40.0	0	00.0	3	23.1	10	21.4	3	16.6	4	18.2	7	17.5
2	22.2	1	10.0	5	55.5	8	61.5	16	39.0	9	50.0	8	36.4	17	42.5
4	44.4	5	50.0	4	44.4	2	15.4	15	36.6	6	33.3	10	45.4	16	40.0
Less favorable position															
Changes in Auxodrome: (Speed of Development)															
3	33.3	3	30.0	1	11.1	2	15.4	9	22.0	3	16.6	2	9.1	5	12.5
1	11.1	2	20.0	0	00.0	3	23.1	6	14.6	3	16.6	2	9.1	5	12.5
5	55.5	5	50.0	8	88.9	8	61.5	26	63.4	12	66.7	18	81.8	30	75.0
Faster auxodrome															
Auxodrome unchanged															
Slower auxodrome															
Changes in Levels per Month: (Rate of Development)															
3	33.3	2	20.0	2	22.2	4	30.8	10	24.4	4	22.2	8	36.4	12	30.0
0	00.0	2	20.0	0	00.0	2	15.4	4	9.8	2	11.1	1	4.5	3	7.5
6	66.7	6	60.0	7	77.8	7	63.8	27	65.9	12	66.7	13	59.1	25	62.5
More than one level per month															
Exactly one level per month															
Less than one level per month															
Changes in Growth Quality: (Speed and Direction of Development)															
3	33.3	2	20.0	0	00.0	1	7.7	6	14.6	2	11.1	1	4.5	3	7.5
0	00.0	2	20.0	0	00.0	1	15.4	3	12.2	0	5.5	1	9.1	1	7.5
0	00.0	1	30.0	0	00.0	1	7.7	2	4.8	1	5.5	1	9.1	2	7.5
More favorable channel; faster schedule															
0	00.0	0	00.0	0	00.0	1	7.7	1	2.4	3	16.6	1	4.5	4	10.0
0	00.0	0	00.0	0	00.0	1	7.7	1	4.8	1	5.5	2	9.1	3	7.5
Less favorable channel; faster schedule															
0	00.0	0	00.0	1	11.1	0	0	1	2.4	0	0	0	0	0	0
3	33.3	0	00.0	4	55.5	6	53.8	13	36.6	5	27.8	6	27.3	11	27.5
Channel unchanged; slower schedule															
0	00.0	0	00.0	1	11.1	1	7.7	2	4.8	0	0	0	0	0	0
3	33.3	5	50.0	3	33.3	1	7.7	12	29.3	6	33.3	10	45.4	16	40.0
Less favorable channel; slower schedule															
Number of Instances of Growth Failure: (Simultaneous Loss in Speed and Direction of Development)															
3	33.3	1	10.0	1	11.1	4	30.8	9	22.0	9	50.0	7	31.8	16	40.0
3	33.3	7	70.0	6	66.7	8	61.5	24	58.5	5	27.8	12	54.5	17	42.5
2	22.2	2	20.0	2	22.2	1	7.7	7	17.1	3	16.6	2	9.1	5	12.5
1	11.1	0	00.0	0	00.0	0	00.0	1	2.4	1	5.5	1	4.5	2	5.0



TABLE III. THE CHANGES IN THE DIRECTION, SPEED, AND RATE OF DEVELOPMENT IN FORTY-ONE TEST AND FORTY-ONE CONTROL CHILDREN DURING THE MILK AND POSTMILK PHASES OF THE STUDY\*

TYPE OF CHANGE	TEST CASES										CONTROL CASES									
	WHOLE MILK					NONFAT MILK					BOYS					GIRLS				
	BOYS		GIRLS		TOTAL	BOYS		GIRLS		TOTAL	NO.		%		%	NO.		%		TOTAL
	NO.	%	NO.	%		NO.	%	NO.	%		NO.	%	NO.	%		NO.	%	NO.	%	
Channel Changes: (Direction of Development)																				
Milk Phase:†																				
←	2	22.2	1	10.0	0	00.0	2	15.4	5	12.2	0	00.0	1	4.5	1	4.5	1	4.5	1	2.5
↔	0	00.0	0	00.0	1	11.1	3	23.0	4	9.8	1	5.6	2	9.1	2	9.1	3	7.5	2	5.0
→	1	11.1	2	20.0	1	11.1	1	7.7	5	12.2	4	00.0	2	9.1	2	9.1	2	5.0	7	17.5
↔↔	0	00.0	1	10.0	3	33.3	1	7.7	5	12.2	4	22.2	3	13.6	3	13.6	7	17.5		
↔↔↔	1	11.1	1	10.0	2	22.2	0	00.0	4	9.8	1	5.6	1	4.5	2	4.5	2	5.0		
↔↔↔↔	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	1	4.5	1	2.5		
↔↔↔↔↔	2	22.2	2	20.0	1	11.1	1	7.7	6	14.6	5	27.7	7	31.8	12	30.0	7	17.5		
↔↔↔↔↔↔	2	22.2	0	00.0	1	11.1	4	30.7	7	17.0	4	22.2	3	13.6	7	17.5	7	17.5		
↔↔↔↔↔↔↔	1	11.1	3	30.0	0	00.0	1	7.7	5	12.2	3	16.7	2	9.1	5	12.5				
Changes in Auxodrome: (Speed of Development)																				
Milk Phase:†																				
←	3	33.3	1	10.0	0	00.0	2	15.4	6	14.6	1	5.6	1	4.5	2	5.0				
↔	1	11.1	0	00.0	0	00.0	3	23.0	4	9.8	0	00.0	0	00.0	0	00.0				
→	4	44.4	3	30.0	2	22.2	3	23.0	12	29.3	0	00.0	1	4.5	1	2.5				
↔	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0				
↔↔	0	00.0	0	00.0	1	11.1	0	00.0	1	2.4	1	5.6	3	13.6	4	10.0				
↔↔↔	0	00.0	1	10.0	0	00.0	0	00.0	1	2.4	0	00.0	0	00.0	0	00.0				
↔↔↔↔	1	11.1	2	20.0	5	55.5	5	38.5	13	31.7	11	61.1	13	59.1	24	60.0				
↔↔↔↔↔	0	00.0	2	20.0	0	00.0	0	00.0	2	4.9	3	16.7	3	13.6	6	15.0				
↔↔↔↔↔↔	0	00.0	1	10.0	1	11.1	0	00.0	2	4.9	2	11.1	1	4.5	3	7.5				
Changes in Levels per Month: (Rate of Development)																				
Milk Phase:§																				
←	3	33.3	1	10.0	1	11.1	3	23.0	8	19.5	1	5.6	3	13.6	4	10.0				
↔	0	00.0	2	20.0	0	00.0	1	7.7	3	7.3	1	5.6	0	00.0	1	2.5				
→	5	55.5	5	50.0	4	44.4	5	38.5	19	46.3	6	33.3	5	22.7	11	27.5				
↔	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0				
↔↔	1	11.1	0	00.0	0	00.0	1	7.7	2	4.9	0	00.0	0	00.0	0	00.0				
↔↔↔	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0				
↔↔↔↔	0	00.0	2	20.0	3	33.3	1	7.7	6	14.6	6	33.3	8	36.4	14	35.0				
↔↔↔↔↔	0	00.0	0	00.0	0	00.0	1	7.7	1	2.4	1	5.6	1	4.5	2	5.0				
↔↔↔↔↔↔	0	00.0	0	00.0	1	11.1	1	7.7	2	4.9	3	16.7	5	22.7	8	20.0				

\*One of the control children did not return for examination during the postmilk phase and, therefore, is not included in the postmilk data.

†+ More favorable channel.

↔ Channel unchanged.

→ Less favorable channel.

†+ Faster auxodrome.

↔ Auxodrome unchanged.

§+ Slower auxodrome.

↔ Made more than one level per month.

→ Made exactly one level per month.

→ Made less than one level per month.

THE EFFECT OF THE MILK SUPPLEMENTS ON THE SPEED OF  
DEVELOPMENT (WETZEL)

*The Milk Period.*—The changes in the speed of development which occurred among the children in the test and control groups during this phase of the study are shown in Figs. 5 and 6. Twenty-two (54 per cent) of the children receiving the supplements moved to faster schedules, two (5 per cent) did not change, and seventeen (41.5 per cent) moved to slower schedules. In contrast, three (7 per cent) of the children in the control group moved to

CHANGES IN AGE SCHEDULES OF DEVELOPMENT  
IN 41 CHILDREN WHO RECEIVED THE MILK SUPPLEMENT  
(MILK AND POST MILK PERIODS)

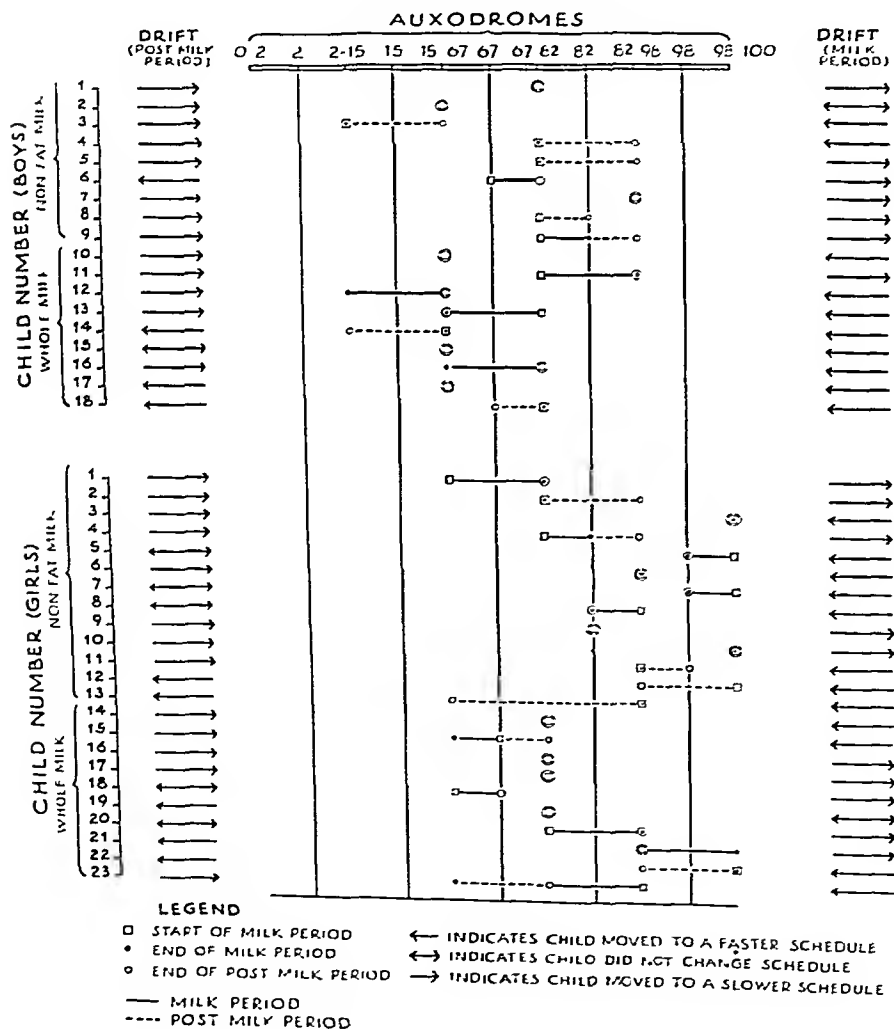


Fig. 5.—The changes in speed of development in the children receiving the milk supplements during the milk and postmilk periods.

faster schedules, four (10 per cent) did not change, and thirty-four (83 per cent) moved to slower schedules. This occurred despite the observation that most of the children in the control group were on slow age schedules of development at the beginning of the study (Fig. 6). The sex differences and the differences observed in the children receiving the whole and nonfat milk are shown in Table I. Improvement in the speed of development was most frequent among the boys who received the whole milk supplement, followed in incidence by the girls who received the nonfat milk, the girls who received the whole milk, the boys who received the nonfat milk, the girls in the control group, and the boys in the control group.

CHANGES IN AGE SCHEDULES OF DEVELOPMENT  
IN 41 CHILDREN IN THE CONTROL GROUP  
(MILK AND POST MILK PERIODS)

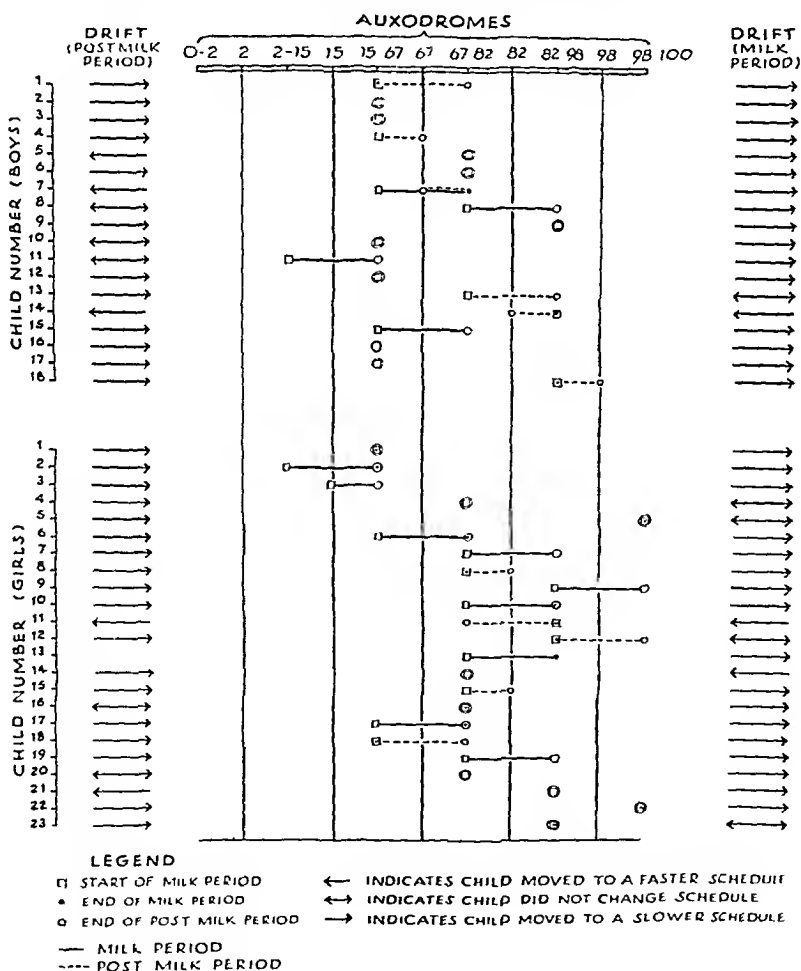


Fig. 6.—The changes in the speed of development in the children in the control group during the milk and postmilk periods.

*The Postmilk Period.*—Figs. 5 and 6 show the findings relative to the changes in the speed of development which occurred in the children in the test group and in the children in the control group during the twelve-month postsupplementation period. Nine (22 per cent) of the children receiving the supplement moved to faster age schedules of development, six (15 per cent) did not change, and twenty-six (63 per cent) drifted to slower schedules. Among the children in the control group the schedules improved in five (12.5 per cent), five (12.5 per cent) did not change, and thirty (75 per cent) moved to slower schedules. These findings are summarized in Table II on the basis of the sex of the child and the type of milk supplement received during the first phase of the study. Improvement in the speed of development was most prevalent among the boys who had received the whole milk supplement, followed in frequency by the girls who had received the whole milk supplement, the boys in the control group, the girls who had received the nonfat milk, the boys who had received the nonfat milk, and the girls in the control group.

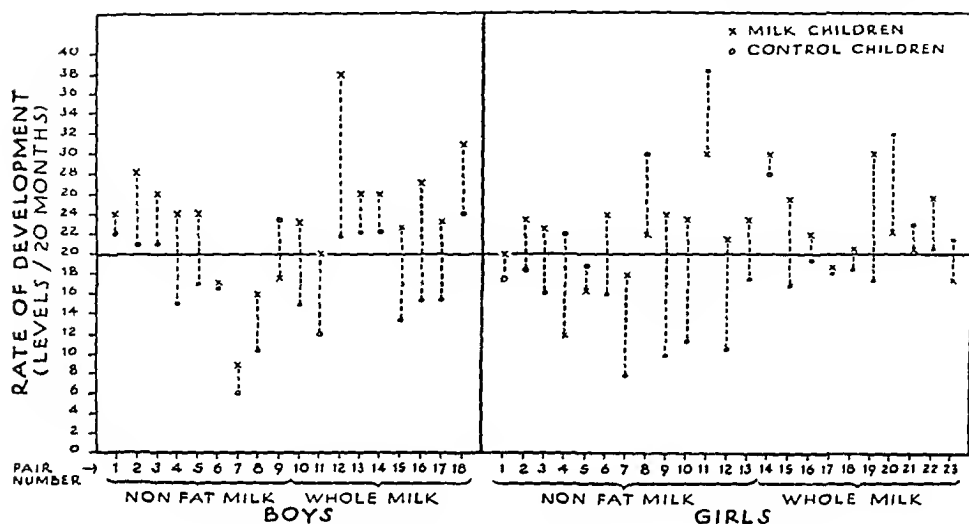
Only six of the twenty-two children in the test group who improved their speed of development during the milk period continued to improve following the withdrawal of the supplement. Four maintained their faster schedules, while twelve moved to slower schedules. Of the three children in the control group whose speed of development improved during the milk period, two continued to shift to faster schedules, while one moved to a slower schedule during the postmilk period (Table III).

#### THE EFFECT OF THE MILK SUPPLEMENTS ON THE RATE OF DEVELOPMENT (WETZEL)

*The Milk Period.*—A summary of the rate of development of the children in the test and control groups during the twenty-month period of supplementation is shown in Fig. 7. Thirty (73 per cent) of the children in the test group proceeded at the rate of more than one level per month during this phase, while two (5 per cent) made exactly one level per month, and nine (22 per cent) progressed at a rate of less than one level per month. In contrast, only sixteen (39 per cent) of the children in the control group made more than one level per month, and twenty-five (61 per cent) made less than one level per month. On the basis of sex of the child and type of milk ingested (Table I) improvement in rate occurred most frequently among the boys receiving the whole milk, followed in descending order by the girls receiving the whole milk, the girls receiving the nonfat milk, the boys receiving the nonfat milk, the boys in the control group, and the girls in the control group.

*The Postmilk Period.*—The changes in the rate of development which occurred in the children in the test and in the control groups during the twelve-month postmilk period are shown in Fig. 7. Ten (24 per cent) of the children in the test group progressed at the rate of more than one level per month, four (10 per cent) made exactly one level per month, and twenty-seven (66 per

THE CHANGES IN THE RATE OF DEVELOPMENT  
(LEVELS / MONTH)  
IN 41 TEST CHILDREN AND 41 CONTROL CHILDREN  
DURING THE 20-MONTH PERIOD OF SUPPLEMENTATION



THE CHANGES IN THE RATE OF DEVELOPMENT  
(LEVELS / MONTH)  
IN 41 TEST CHILDREN AND 40 CONTROL CHILDREN  
DURING THE 12-MONTH POSTSUPPLEMENTATION PERIOD

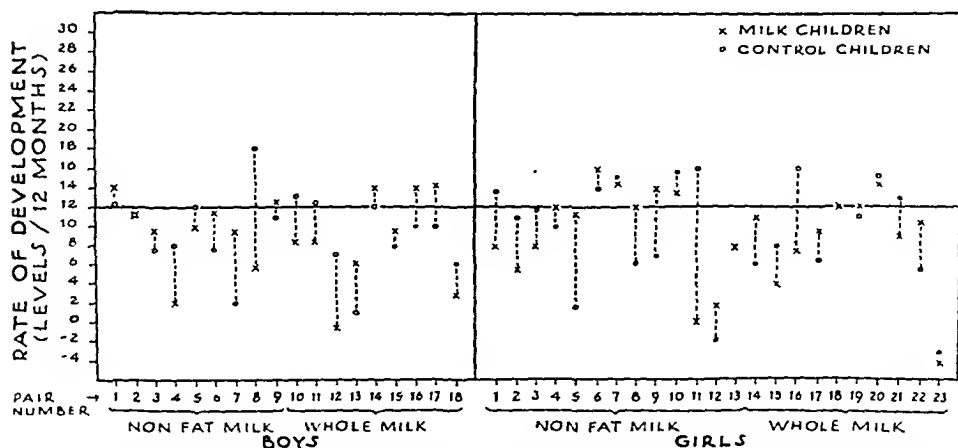


Fig. 7.—The changes in the rate of development (levels per month) in the children receiving the milk supplements and in the children in the control group during the milk and postmilk periods.

cent) made less than one level per month. Twelve (30 per cent) of the children in the control group made more than one level per month, three (7.5 per cent) made exactly one level per month, and twenty-five (62.5 per cent) made less than one level per month during this phase of the study. Table II shows a summary of these findings. Improvement was most prevalent among the girls in the control group, followed in frequency by the boys who had received the whole milk supplement, the girls who had received the nonfat milk supplement, the boys who had received the nonfat milk supplement, the boys in the control group, and the girls who had received the whole milk supplement.

Of the thirty children in the test group who made more than one level per month during the milk period, eight continued to make more than one level per month, three made exactly one level per month and nineteen made less than one level per month after the supplement was discontinued. By comparison, four of the sixteen children in the control group who made more than one level per month during the milk period, continued at the rate of more than one level per month, one made exactly one level per month, while eleven made less than one level per month during the postmilk phase of the study (Table III).

#### THE EFFECT OF THE MILK SUPPLEMENTS ON THE QUALITY OF GROWTH (WETZEL)

*The Milk Period.*—The changes in the quality of growth in the individual children in the test and control groups during the supplementation phase of the study are shown in Table I. In eleven (27 per cent) of the children receiving the supplements the quality of growth improved in both of its components (speed of development and direction of development); five (12 per cent) improved in one component while maintaining their position in the other; eleven (27 per cent) improved in one component but underwent undesirable changes in the second; five (12 per cent) underwent a detrimental change in one component while the second remained unchanged; and nine (22 per cent) failed to maintain both their speed and direction of development, a factor suggestive of poor quality growth. None of the children in the control group improved in both components of growth quality simultaneously during this period. Three (7 per cent) improved in one and maintained their position in the other; one (2 per cent) did not change in either component; six (15 per cent) improved in one component but lost ground in the second; ten (24 per cent) fell off in one component while maintaining their positions in the second; and twenty-one (51 per cent) fell off in both components. The quality of growth of the older children, in general, was superior to that of the younger children, a finding which was noted in children in both the test and control groups during this period.

*The Postmilk Period.*—The changes in the quality of growth which occurred in the children in both the test and control groups in the postmilk period are presented in Table II. In six (15 per cent) the quality of growth

improved in both components, five (12 per cent) improved in one and remained unchanged in the other, in one (2 per cent) there was no change in either speed or direction of development, two (5 per cent) improved in one component but fell off in the other, fifteen (37 per cent) lost position in one component and remained unchanged in the second, while twelve (29 per cent) fell off in both speed and direction of development. In contrast, the corresponding values for the forty control children were three (7.5 per cent), three (7.5 per cent), four (10 per cent), three (7.5 per cent), eleven (27.5 per cent), and sixteen (40 per cent).

Four of the eleven children in the test group who improved in both speed and direction of development continued their improvement in both of these components of growth quality throughout the postmilk phase, while four lost both speed and direction, one maintained the speed and direction achieved during the period of supplementation, one improved in direction but lost speed, and one maintained direction but lost speed.

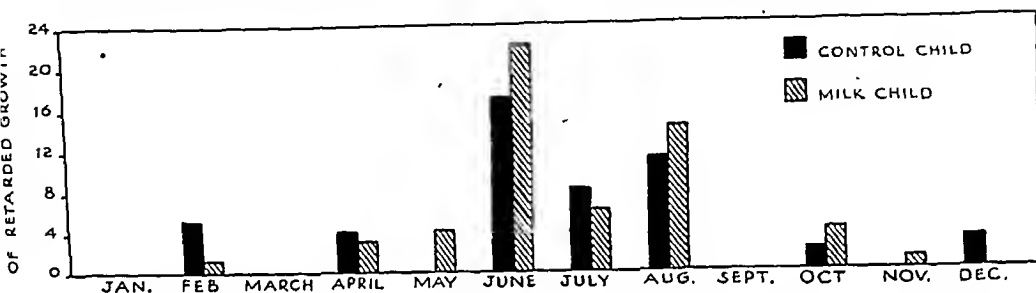
#### THE EFFECT OF THE MILK SUPPLEMENTS ON THE INCIDENCE OF EPISODES OF RETARDED GROWTH

*The Milk Period.*—The incidence of episodes of retarded growth in the children in the test and control groups during the twenty-month supplementation period is shown in Table I. Each instance of retarded growth was represented on the Grid by a drift down-channel, accompanied by an auxodromic lag which exceeded the limits of tolerance. Eleven (27 per cent) of the children in the test group did not show any episodes of growth failure, while fourteen (34 per cent) underwent one instance of retarded growth, eleven (27 per cent) underwent two, four (10 per cent) underwent three, and one (2 per cent) underwent four. While eight (19.5 per cent) of the children in the control group were free from episodes of retarded growth, thirteen (32 per cent) experienced one, eighteen (44 per cent) experienced two, and two (5 per cent) experienced three. Fig. 8 reveals that the incidence of retarded growth in both the test and control groups during the milk period was greatest in June, July, and August. In eight instances the episodes of growth failure in the children in the test group occurred concomitantly with bouts of infectious disease. Infectious disease accompanied episodes of growth failure in three of the children in the control group.

*The Postmilk Period.*—The incidence of episodes of retarded growth during the twelve-month postmilk period is shown in Table II. Nine (22 per cent) of the children in the test group made unimpeded progress, twenty-four (58.5 per cent) underwent one instance of retardation, seven (17 per cent) underwent two, and one (2 per cent) underwent three. In contrast, sixteen (40 per cent) of the children in the control group made unimpeded progress during this period, seventeen (42.5 per cent) underwent one instance of retardation, five (12.5 per cent) underwent two, and two (5 per cent) underwent three. The highest incidence of retarded growth in both the test and control groups during this phase occurred in June, August, and October (Fig. 8).

Infectious disease accompanied episodes of growth failure in three instances in the test group and in six instances in the control group. The incidence of growth failure was greater in the younger children in both groups than in the older children, a finding which was observed in both the milk and postmilk periods.

THE MONTHLY DISTRIBUTION OF THE EPISODES OF RETARDED GROWTH IN 41 TEST CHILDREN AND 41 CONTROL CHILDREN DURING THE 20-MONTH PERIOD OF SUPPLEMENTATION



THE MONTHLY DISTRIBUTION OF THE EPISODES OF RETARDED GROWTH IN 41 TEST CHILDREN AND 40 CONTROL CHILDREN DURING THE 12-MONTH POST SUPPLEMENTATION PERIOD

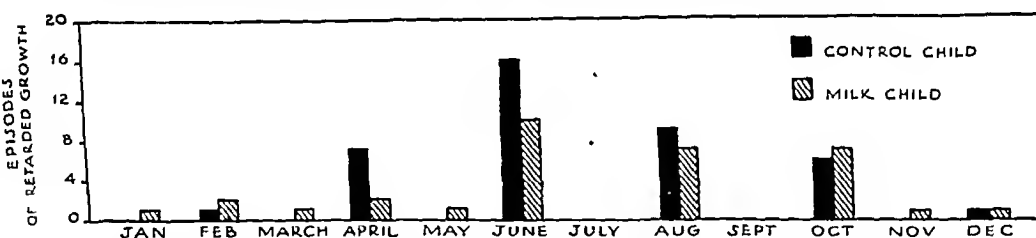


Fig. 8.—The incidence of episodes of retarded growth in the children receiving the milk supplements and in the children in the control group during the milk and postmilk periods. Note the seasonal variations in the incidence of retarded growth in both groups of children.

#### DISCUSSION

Since by the Grid technique each child is his own basis for comparison, the findings reported in this paper include only those derived from the individual child in each pair rather than from each pair as a single unit.

In analyzing the Grid findings for each child during each phase of the study, it is apparent that the most pronounced difference between the growth patterns of the children in the test and control groups existed in their respective rates of development. The rapid rate of development characteristic of the great majority of the children in the test group during the milk period was dependent to some extent upon the type of milk provided in the supplement. The number of children involved, however, is too small to permit a distinction between the relative effectiveness of the whole and nonfat milk supplements on the basis of the Grid data alone. Only nine of the forty-one children who received the milk supplement progressed at a rate of less than one



isodevelopmental level per month, as contrasted with twenty-five of the forty-one children who did not receive the milk supplement. In the Grid technique the rate of development is measured in terms of the number of isodevelopmental levels gained per month. The isodevelopmental level reached by a child is, in turn, dependent upon his height and weight. It would appear, therefore, that the nutrients supplied by the milk supplements were implicated in some manner with the rapid increases in height and weight observed in the children in the test group. The withdrawal of the supplement resulted in a decline in the rate of development in twenty-two (73 per cent) of the thirty children in whom a rate exceeding one level per month had been noted during the milk phase of the study.

A second significant effect of the milk supplement was the improvement in the speed of development (determined from the changes in the age schedules of development) of many of the children in the test group during the milk phase of the study. Here again this finding is emphasized by the failure of sixteen (73 per cent) of the twenty-two children in this group, whose speed of development increased during the milk period, to continue the improvement when the supplement was withdrawn. In the Wetzel formulation, the speed of development is dependent upon the age of the child and the isodevelopmental levels reached by the child at successive examinations. While it may appear that increases in the *speed* of development should have paralleled those noted for the *rate* of development, it must be recalled that not all of the children in the test group were in the same phase of growth at the same time throughout the study, but that they ranged in growth phase from childhood through adolescence. Since the age schedules of development of the Wetzel Grid are constructed in acknowledgment of the differences in speed during the various phases of growth, it would seem that this factor may account for the lower incidence of increases in speed of development among the children in the test group when compared with the changes in rate of development.

While a significantly larger number of the children in the test group improved in their direction of development as contrasted to the children in the control group, this response was not nearly as widespread as that observed for the rate and speed of development. Because of the width of the Grid channels, the increases in height and weight required to effect a favorable change in the direction of development (as measured by the relation of the child's channel curve to the incline of the channel system) are considerably greater than those required to produce an increase in the rate and speed of development in the same child. Despite the fact that the majority of the children in the test group followed the M to B<sub>1</sub> physique channels on the Grid (Fig. 3), the increases in height and weight in these children during the milk period were insufficient to improve materially the direction of development in twenty-seven of the forty-one cases.

In the Wetzel formulation, the quality of growth is dependent upon the direction of development and the speed of development. The effect of the

milk supplements on each of these components individually has been discussed in detail in the preceding paragraphs. Suffice it to say that whereas the quality of growth improved in eleven of the children in the test group during the supplementation period, this response was not observed in any of the children in the control group. When the supplement was withdrawn only four (37 per cent) of the eleven children continued their improvement. The indications are, therefore, that nutritive failure has a pronounced deterrent effect upon the quality of growth.

An analysis of the number of instances of retarded growth in both groups of children during both phases of the study reveals that for the most part the frequency of episodes of retarded growth followed the seasonal distribution reported in a previous publication.<sup>5</sup> While no significant differences were observed between the two groups of children, as groups, in either phase, it was noted that the instances of retarded growth declined in number as the children approached physical maturity. It would appear that since the children with nutritive failure were, in the main, on progressively slower age schedules of development (Figs. 5 and 6), a point was eventually reached at which the calorie needs required to maintain the slow schedules of development were fulfilled by even a substandard food intake.

#### SUMMARY AND CONCLUSIONS

Eighty-two children were paired on the basis of history and evidence of nutritive failure, sex, roentgenographic analyses of the hand, wrist, and forearm, phase of growth, general body type, freedom from contagious and infectious disease and allergy to cows milk, and accessibility of the home and cooperation of the parents. One child in each pair was given a supplement of the equivalent of one quart of either reconstituted whole milk ( $4\frac{1}{4}$  ounces of milk solids) or nonfat milk (3 ounces of milk solids) each day, six days per week, for a period of twenty months. Twenty-two children (nine boys and thirteen girls) received the nonfat milk, while nineteen children (nine boys and ten girls) received the whole milk. No changes other than the addition of the milk supplement to the daily dietary of one child in each pair were made in the lives of any of the children selected for this study except those changes which were completely voluntary. Each child, with the exception of one child in the control group, was studied for an additional twelve months after the supplement was discontinued.

This report is confined to a summation of some of the changes in the growth progress of both groups of children which occurred during the milk and postmilk phases of the investigation as measured by the Wetzel Grid. The findings include only those derived from the individual child in each pair rather than from each pair as a single unit. They constitute the following:

1. Only sixteen (39 per cent) of the children who did not receive the milk supplement progressed at a rate of more than one isodevelopmental level per month during the milk phase, as contrasted with thirty (73 per cent) of the children who received the milk supplement.

Only eight (27 per cent) of the thirty children in the test group who had progressed at a rate of more than one isodevelopmental level per month during the milk phase continued to do so in the postmilk period.

2. Only three (7 per cent) of the children who did not receive the milk improved their speed of development during the milk phase, as contrasted with twenty-two (54 per cent) of the children who received the milk supplement.

Only six (27 per cent) of the twenty-two children in the test group who improved their speed of development during the milk phase continued to do so during the twelve-month postsupplementation period.

3. Only six (15 per cent) of the children in the control group improved their direction of development during the milk phase, as contrasted with fourteen (34 per cent) of the children who received the milk supplement.

Only five (36 per cent) of the fourteen children in the test group who had improved their direction of development during the milk phase continued to do so in the postmilk phase.

4. None of the children in the control group improved their quality of growth during the milk phase of the study, while eleven (27 per cent) of the children who received the milk supplement improved in this respect during the same period.

Only four (36 per cent) of the eleven children in the test group who had improved their quality of growth during the milk phase continued to do so following the withdrawal of the supplement.

5. No attempt was made in this report to correlate the Grid findings alone with the type of milk supplement because of the small number of children receiving the whole milk supplement (nine boys and ten girls) and the non-fat milk supplement (nine boys and thirteen girls).

6. The Wetzel Grid proved to be a useful method for measuring certain changes in the growth progress of children with chronic nutritive failure when a known amount of milk was added to their daily dietaries. The growth of every child, however, is a phenomenon specific for that child, and such aids as the Wetzel Grid must be interpreted in the general light of the sum total information which can be acquired from the large variety of factors which influence growth progress.

We are indebted to Mrs. Elizabeth Slater Seay and Miss Jean Grant for making the dietary assessments and to Miss Catherine Currie, Miss Jo Gilley and James O. Harbour for technical assistance.

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## ANTI-HISTAMINIC DRUGS IN PEDIATRIC ALLERGY

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**A**PPROXIMATELY 10 per cent of the population develop the common major allergies. Of these, one-third begin to have symptoms within the first decade. The practice of allergy, therefore, is an integral part of the practice of pediatrics. Without doubt, the early recognition and institution of adequate therapy in allergic children is imperative, first, because it is therapeutically satisfactory, and second, because diseases of sensitivity, if allowed to carry on unchecked, may lead to irreversible pathologic changes which are difficult to treat successfully.

Most of the allergic states may be seen in children. There are some differences, however, in their diagnosis and management. Nasal allergy in the child often is mistaken for the common cold. Bronchial asthma, which may start as an allergic cough, may be mistaken for a recurrent infective bronchitis. Disfigurement of the face in allergic rhinitis, or disfigurement of the chest in bronchial asthma is always a possible complication of untreated respiratory allergy. Allergic conditions may not only make children irritable but may also affect their growth.

Good therapeutic results, however, usually are obtained in allergic children. As a rule no irreversible pathology has been created and the children respond quickly to correct therapy. However, symptomatic relief frequently is necessary. This not only creates confidence but also if the irritability of the child is decreased, allergic investigation is made much easier. Occasionally it is necessary to give some form of adjunct therapy to a child whose condition does not respond to hyposensitization treatment. It is in these instances that anti-histaminic drugs have proved so useful.

### ROLE OF HISTAMINE IN ALLERGY

Anaphylaxis and certain allergic manifestations are analogous immunologically in many respects. The manifestations of both are due to an antigen-antibody union which irritates the cells of certain tissues, which are referred to as shock tissues. As a result of such irritation there occurs in animals smooth muscle spasm (bronchioles in the guinea pig and media of arterioles in the rabbit); in man there occurs both smooth muscle spasm and dilatation and increased permeability of capillaries. For a long time investigators have tried to find out just what produces this irritation. This question was finally answered by Lewis, who concluded as a result of his investigations that the antigen-antibody union releases in the tissues either histamine or a histaminelike substance and that it is this chemical which produces reversible tissue changes charac-

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teristic of anaphylaxis or allergy. He pointed out the similarity between histamine shock and anaphylactic shock, as well as the similarity between the positive skin reactions obtained from the intradermal injection of histamine and the injection of the specific allergen in a sensitive individual.

Histamine has the property of causing contraction of the guinea pig uterine strip and produces a fall in the peripheral blood pressure of the cat. Injected intradermally in man, it produces a local change which has been described as the triple response of Lewis. It consists of (1) erythema, (2) flare, and (3) whealing. This triple response is identical with that produced on the skin of a dermatographic patient by mechanical irritation such as scratching. The administration of histamine in large doses produces profound vasodilatation with loss of circulating fluid and reduction in cardiac output. Histamine apparently acts directly on capillaries without the intervention of the nervous mechanism, dilating these capillaries and producing increased capillary permeability. This effect does not involve equally all the smaller arterioles and capillaries. For example, while the vessels of the face and neck are dilated, those in the extremities are contracted, accounting for the marked difference in the skin temperature of the extremities and of the face after histamine administration. Salivary, gastric, and bronchial mucous glands are stimulated. The blood pressure is lowered. The smooth muscle of the bronchi, intestines, and uterus is contracted. Clinically, there occurs dizziness, headache, and flushing of the face. Symptoms resembling those of histamine administration may result in patients with allergy to physical agents. These include, as is shown by one of our cold-sensitive patients, local whealing on contact with cold followed by flushing of the face, dizziness, and lowered blood pressure.

In view of this all-important role played by histamine or an H-like substance in the mechanism of allergic manifestations, it is logical that efforts should have been directed for many years toward the discovery of some agent which would combat this histamine-like influence on the tissues. Such an agent would have to possess the property of either (1) destroying histamine chemically, (2) decreasing the susceptibility of the shock tissue to histamine, or (3) in some way interfering between the union of antigen and antibody so that this union will not result in histamine liberation and (4) stimulating the sympathetic nervous system.

The following agents have been tried with disappointing results as antihistaminic agents.

#### HISTAMINASE

Best and McHenry showed in 1930 that extracts of fresh tissues such as the kidney and the intestines contain an enzyme and that this enzyme can destroy histamine in the test tube. It was natural to assume that the introduction of this enzyme (histaminase) into the body of an allergic patient in large quantities might help counteract the effects of histamine. Extensive clinical use of histaminase in various allergic disorders such as urticaria, hay fever, and asthma prove this drug to be of very little value. Administration of the drug does not interfere with the direct skin test or with the passive transfer reaction.

## HISTAMINE-AZO-PROTEIN (HAPAMINE)

Hapamine has had wide usage in the treatment of allergic disorders. Histamine is a substance of small molecular weight, rapidly dialyzable and in itself not antigenic. However, it can be rendered antigenic by combining it or conjugating it with some protein (haptene). Working with this combination (histamine-azo-protein), Fell demonstrated that precipitins are formed by injecting rabbits with this substance and that these precipitins are specific for the histamine part of the compound. The administration of histamine-azo-proteins in man stimulates the formation of specific precipitins in the serum. It is also shown that histamine may be neutralized in vitro by the sera of patients treated with histamine-azo-protein. However interesting these laboratory results may be, our experience and that of others indicates that histamine-azo-protein (Hapamine) is not effective in the treatment of allergic disorders.

## HISTAMINE

An attempt has been made to increase histamine tolerance by the administration of increasing doses of histamine. This has been carried out either by the subcutaneous administration of a solution of histamine acid phosphate, or by the administration of 2.75 mg. of histamine acid phosphate in 300 c.c. of normal saline intravenously daily for six successive days. It is interesting to point out that the administration of histamine subcutaneously or intravenously does not reproduce clinical allergic manifestations such as asthma or hay fever in an allergic individual, nor is there any agreement of opinion that this form of therapy either helps to increase the tolerance of the patient to histamine or that it results in any clinical benefit. Histamine therapy is said to be effective in the treatment of a certain type of chronic vascular headache (histamine cephalgia), although the mechanism of its effect is not clearly understood.

## ANTERGAN AND NEO-ANTERGAN

French investigators were working as early as 1932 on a series of chemicals for which the tissues would have a greater affinity than for histamine. Antergan (N-phenyl-N'-benzyl-N-dimethylethylenediamine) and later Neo-Antergan ( $C_{21}H_{27}N_3O_5$ ) (Ethylenediamine, N-p-methoxybenzyl-N', N'-dimethyl-N-2-pyridylmalate) were finally discovered. Both of these are potent antihistaminic drugs in that if they are injected subcutaneously into guinea pigs they will protect the animal against the fatal result obtained from the administration of many times the fatal dose of histamine. Of the two, Neo-Antergan is more potent and less toxic. The drug has been introduced recently on the American market but is still being investigated. The dose is 50 to 100 mg. and the drug is available in coated tablets.

## AMERICAN ANTIHISTAMINIC DRUGS

These drugs were followed later by Benadryl and Pyribenzamine, which were produced in this country. The latter agents have received attention for their clinical value in certain allergic states. However useful these drugs may

be, they have certain disadvantages. They often cannot be used in adequate doses in pediatric practice because of their unpleasant and frequent side reactions which include drowsiness, headache, and dizziness.

#### NEOHETRAMINE

Neohetramine, a recent histamine antagonist, has been shown by us to have potent antihistaminic, antianaphylactic, and antiwhealing properties. Studies with both animals and adult humans illustrate its low toxicity.

The therapeutic results in the symptomatic treatment of allergic diseases in the adult by the use of Neohetramine compare favorably with the results obtained from other similar drugs. Reference to Table I indicates that the best results were obtained in hay fever, allergic rhinitis, and urticaria.

TABLE I. CLINICAL EFFECTS OF NEOHETRAMINE ON ADULTS

NO.	DIAGNOSIS	NONE (%)	SLIGHT (%)	MODERATE (%)	COMPLETE RELIEF (%)
124	Hay fever	18	22	27	33
41	Allergic rhinitis	20	27	24	27
33	Bronchial asthma	37	24	27	12
11	Atopic dermatitis	18	73	9	0
20	Urticaria	25	25	20	30
6	Migraine	17	33	0	50
8	Contact dermatitis	0	38	50	12

#### CHEMICAL EFFECTS OF NEOHETRAMINE ON CHILDREN

The present clinical study on children was carried on with Neohetramine (2-(N-methoxybenzyl-N-dimethylamino-ethyl)-aminopyrimidine monohydrochloride). Neohetramine is available in the following forms: elixir Neohetramine 25 mg. to the dram, and in the form of tablets of 50 mg. and 100 mg. doses. A total of 232 infants and children received Neohetramine for the symptomatic relief of various allergic disorders, for a period ranging from two weeks to four months. The patients varied in age from 6 months to 12 years. The dose was one dram of the elixir every four hours for infants up to 4 years of age and 50 mg. every four hours for older children. The drug was administered only when symptoms were present. When relief was obtained from a given dose, it lasted, as in the case of other antihistaminic drugs, for a period of three to six hours. When effective, one dose taken at bedtime would quiet the child and enable him to sleep for the night. The results as seen in Table II were divided into no relief, moderate, and complete relief from symptoms.

Placebo controls were used in a control group of ten patients with allergic rhinitis, twelve cases of seasonal hay fever, thirteen cases of urticaria, twenty cases of bronchial asthma, and five cases of atopic dermatitis. In many instances the drug was discontinued and then readministered a few days later in order to observe its repeated effect.

Children suffering with hay fever received the drug throughout the duration of the season. In patients with allergic rhinitis, bronchial asthma, and urticaria, its administration was continued over periods of two to four



TABLE II. NEOHETRAMINE IN ALLERGIC CHILDREN

	TOTAL NO. PATIENTS	NO RELIEF		MOD. RELIEF		MARKED RELIEF		SIDE ACTIONS
		NO.	%	NO.	%	NO.	%	
Allergic rhinitis	61	11	17	22	35	28	48	6
Hay fever	47	5	10	17	36	25	54	4
Urticaria and Angio- neurotic edema	22	3	14	7	31	12	55	3
Bronchial asthma	66	46	70	14	21	6	9	4
Atopic dermatitis	21	10	50	8	40	3	10	1
Contact dermatitis	9	7	78	1	11	1	11	0
Physical allergy	3	—	—	—	—	3	100	0
Gastrointestinal allergy	3	1	33	2	66	0	—	0

months. This was done in order to study the therapeutic effect of the drug, but also in order to discover possible toxic influences of its prolonged administration. Repeated urine, blood count, blood chemistry, and electrocardiographic examinations failed to reveal any evidence of such toxic effects.

*Allergic Rhinitis.*—A total of sixty-one children with allergic rhinitis received the drug for periods ranging from two weeks to two and one-half months. Of this number, 17 per cent received no relief, 35 per cent had moderate relief, and 48 per cent had complete relief of symptoms while the drug was given. The nasal obstruction and rhinorrhea as well as the itching were relieved when the drug was therapeutically effective.

*Hay Fever.*—A total of forty-seven children suffering with seasonal hay fever received Neohetramine in amounts referred to above for various intervals during the duration of the hay fever season. Fourteen of these children either had no preseasonal pollen therapy or the amount of treatment received by them was considered inadequate. Only 10 per cent of the total number of patients receiving Neohetramine did not respond. Thirty-six per cent had moderate relief and 54 per cent were so completely relieved that the patients asked for a refill of their prescription when the available supply of the drug was exhausted. This relief was obtained equally in the treated and untreated hay fever group, that is, in patients whose symptoms were mild and who received proper prophylactic pollen therapy, as well as in the untreated group in which the symptoms were severe. No differences in the effectiveness of the drug were observed in those sensitive to grasses, fungi, or ragweed.

*Urticaria and Angioneurotic Edema.*—The results in a total of twenty-two children with urticaria were as follows: (1) 14 per cent were not relieved; (2) 31 per cent were moderately relieved; and (3) 55 per cent were completely relieved of symptoms. The drug does not prevent the recurrence of urticaria but brings about quick relief once the lesions appear.

*Bronchial Asthma.*—Sixty-six patients with bronchial asthma were studied. These were for the most part due to allergy to exogenous substances and not accompanied by any complications. The drug was given in adequate doses over a period of several weeks at a time and then repeated at a later date. The results were equally disappointing in asthma of various degrees of severity. Seventy per cent of all patients were not relieved at all, 21 per cent were moderately relieved, and 9 per cent were markedly relieved.

*Atopic Dermatitis.*—The clinical results in a total of twenty-one patients with atopic dermatitis were studied. Fifty per cent of this group were not relieved at all. Forty per cent seemed to have less itching and 10 per cent claimed complete relief. It is difficult to interpret these results because other treatment was used concomitantly and because it was difficult to evaluate psychogenic factors. Neohetramine ointment (2 per cent) was also used locally in these cases with results which are not too encouraging. Many of the twelve children in whom local application of the drug was employed stated that they obtained some relief at first, but later the annoying pruritis reappeared and in none of the cases was the dermatitis improved as compared with other involved areas which remained untreated. This experience is similar to that obtained with the local application of other antihistaminic drugs.

*Contact Dermatitis.*—Neohetramine did not offer much relief in contact dermatitis, regardless of whether the drug was administered orally or applied locally. A total of nine children were studied. Four of these had poison ivy dermatitis. Seventy-eight per cent were not at all benefited. Eleven per cent were moderately and eleven per cent were markedly improved. This series is small but sufficient to warrant the above conclusions.

*Physical Allergy.*—Of three children studied, two were sensitive to cold and one was allergic to sunlight. All of these patients were improved symptomatically.

*Gastrointestinal Allergy.*—Three children suffering with gastrointestinal symptoms due to food allergy were improved symptomatically by Neohetramine. One child sensitive to milk could take moderate quantities of milk after the drug was taken previously.

*Side Reactions.*—Of the 232 patients who used Neohetramine, only 18 or 8 per cent had any side reactions. This is somewhat less than observed in adults. These reactions consisted of restlessness, insomnia, constipation, rhinorrhea, drowsiness, and headache in the order of frequency. In only four of these children was it necessary to discontinue the drug because of these reactions. This percentage of side reactions is certainly a great deal lower than that found from the use of benadryl and pyribenzamine as well as many other antihistaminic drugs.

#### CONCLUSIONS AND SUMMARY

Neohetramine is a potent new antihistaminic drug. The therapeutic results obtained from the use of this drug in the symptomatic treatment of allergic disorders in infants and children of all ages compares favorably with the results obtained from other antihistaminic agents.

It is interesting to point out that some children will be relieved by one antihistaminic drug and others by a different drug. The side reactions obtained from Neohetramine are definitely lower than those observed from the use of other drugs and therefore its use is safer in children. No serious side reactions or fatalities have been reported. Careful observation of children receiving the

drug over periods as long as three months fail to reveal any effect on blood pressure, pulse rate, urine, or blood count

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## LEUCEMIA IN CHILDHOOD

### A CLINICAL AND ROENTGENOGRAPHIC STUDY OF SEVENTY-TWO CASES

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**L**EUCEMIA in childhood is a fatal systemic disease affecting chiefly the blood forming organs of the body. At some time during the course of the disease, abnormal leucocytes can be demonstrated in the peripheral blood, the bone marrow, or both. The cause of the disease is not known but it is generally accepted that leucemia is related to the neoplastic group of conditions.

The purpose of this paper is to present a review of the clinical and roentgenographic findings in a large series of cases of leucemia occurring in infants and children.

#### MATERIAL

The patients comprising this study were observed on the pavilions of the Children's Clinic at the New York Hospital from September, 1932, to June, 1948. During this period the diagnosis of leucemia was made for seventy-two infants and children on the basis of clinical, hematologic or autopsy findings either singly or in combination.

#### RESULTS

*Incidence.*—Leucemia is relatively uncommon in infants and children. During the period covered in the study, the incidence was 0.42 per cent of all admissions to this general pediatric service. Despite this low incidence, leucemia, occurring in seventy-two juvenile patients, was the most frequently encountered malignant condition. It surpassed in number the combined malignant tumors of the brain (17), kidney (9), adrenal (6), eye (4), and bone (2), as well as the related lymphoblastomas; Hodgkin's disease (9), and lymphosarcoma (2).

*Sex and Age Distribution.*—The sex and age distribution of the seventy-two patients is presented in Table I. Thirty-eight, or 52.7 per cent, of the patients were boys. The usually reported predominance of males in the early years of life was not noted. Actually, during the first four years girls showed a slightly higher incidence of the disease. In the second five years the number in girls fell and, conversely, the incidence in boys showed an increase after the first semidecade. The figures for the age group between ten and fifteen years are incomplete since children over the age of 13 years are not admitted to the pediatric service. Despite the incompleteness in the third semidecade, there appeared to be a continuing decrease in the incidence among girls and an increase among boys.

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TABLE I. SEX AND AGE (SEVENTY-TWO CASES)

AGE (YR.)	MALE	FEMALE	NO. CASES	PER CENT	
				MALE	FEMALE
0-1	1	1	2	50.0	50.0
1-2	1	4	5	20.0	80.0
2-3	6	7	13	46.2	53.8
3-4	4	6	10	40.0	60.0
4-5	6	1	7	85.7	14.3
	18	19	37	48.65	51.35
5-6	5	2	7	71.4	28.6
6-7	5	4	9	55.6	44.4
7-8	2	3	5	40.0	60.0
8-9	0	0	0	—	—
9-10	2	3	5	40.0	60.0
	14	12	26	53.9	46.1
10-11	2	2	4	50.0	50.0
11-12	1	0	1	100.0	—
12-13	3	1	4	75.0	25.0
	6	3	9	66.67	33.33
Total	38	34	72	52.70	47.30

LEUKEMIA  
AGE INCIDENCE (72 CASES)

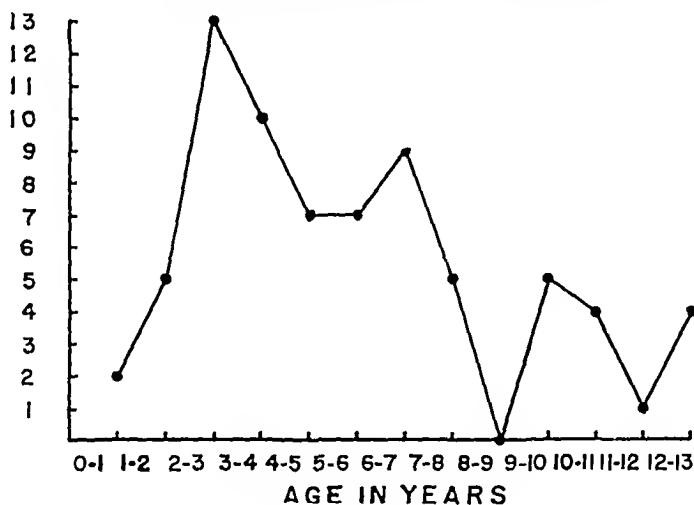


Fig. 1.

The age incidence is plotted in Fig. 1. It ranged from 10 months to 12¾ years. The peak was in the third year of life and the majority of cases occurred in the first five years. Except for a secondary rise of questionable significance in the seventh year, the incidence tended to decrease steadily after the third year.

The figures for sex and age distribution in this series are similar to those reported by Cooke<sup>1</sup> in 1942 in his review of 1,500 cases of childhood leucemia.

TABLE II. DURATION OF LEUKEMIA (THIRTY-NINE PATIENTS)

TIME (MO.)	NO.	%
0-1	2	
1-2	6	
2-3	6	
3-4	2	
4-5	8	
5-6	3	
Subtotal	27	69.2
6-7	3	
7-8	1	
8-9	1	
9-10	2	
10-11	0	
11-12	1	
Subtotal	8	20.5
Total	35	89.7
Over 12	4	10.3

*Duration.*—The course of leucemia in childhood is characteristically acute, rapidly progressive, and fatal within a few weeks or months from the onset. The duration of the disease, as estimated from the time of appearance of the first symptom to the time of death of the patient, is shown for thirty-nine patients in Table II. Thirty-five patients, or 89.7 per cent, died within one year; twenty-seven, or 69.2 per cent, within six months of the onset of symptoms. The range was two weeks to two ten/twelve years. Three patients survived one and one-half years or longer. Hematologic and necropsy findings revealed that the latter had a chronic form of leucemia.

*Clinical and Hematologic Classification.*—The acute form of leucemia is most frequent during childhood, as shown in Table III. Chronic forms do occur but they are rare. In this series, sixty-nine, or 95.8 per cent, of the patients were classified as having acute leucemia on the basis of the clinical course and hematologic studies; three, or 4.2 per cent, were diagnosed as chronic.

TABLE III. CLASSIFICATION—CLINICAL AND HEMATOLOGIC (SEVENTY-TWO CASES)

CLASSIFICATION	NO.	%
<i>Acute</i>	69	95.8
Lymphoid	46	
Myeloid	22	
myeloblastic (16)		
myelocytic (6)		
Monocytoid	1	
<i>Chronic</i>	3	4.2
Lymphoid	1	
Myeloid	2	
Total	72	100.0

Hematologic classification was made in the conventional manner on the type of abnormal leucocyte appearing in the peripheral blood, the sternal marrow, or both. The high frequency of diagnosis of the acute myeloid type of leucemia is thought to be related to the introduction in 1937 of sternal marrow aspiration and to the increased ability of members of the staff to recognize abnormal leucocytes.

*Symptoms and Physical Findings.*—It is recognized generally that childhood leucemia has no characteristic symptom complex and that it is often extremely protean in its early manifestations, closely simulating many of the acute and subacute diseases of this period.

Fourteen, or 19.2 per cent, of the seventy-two patients gave a history of infection prior to the onset of the disease. With one exception the infection was acute tonsillitis or pharyngitis. In this exception, symptoms of leucemia followed scarlet fever. This low incidence of preceding infection lends little support to the infectious theory of the cause of leucemia.

A number of symptoms such as fever, malaise, fatigue, loss of appetite, and irritability are nonspecific and are common to many childhood diseases. There is, however, a group of relatively constant symptoms resulting from involvement of the various organ systems by leucemic cells which is of aid to the clinician in diagnosis. Chief among these symptoms are pallor, hemorrhagic manifestations, bone and joint pain, and enlargement of the lymph nodes. Table IV presents the most frequently encountered symptoms in the seventy-two patients studied.

TABLE IV. SYMPTOMATOLOGY (SEVENTY-TWO CASES)

SYMPTOM	NO.	SYMPTOM	NO.
Fever	44	Joint pain	11
Pallor	40	Enlarged cervical nodes	11
Hemorrhagic tendencies	38	Joint swelling	11
Loss of appetite	24	Weight loss	10
Fatigue	22	Facial edema	5
Bone pain	17	Vomiting	3
Preceding infection	14	Irritability	3
Abdominal pain	12	Enlarged axillary nodes	2

The physical findings in our patients differed in no essential respects from those described in standard pediatric textbooks.<sup>2, 3</sup> It is of interest that the presence of fever, bone and joint swelling and tenderness, and a systolic heart murmur in the absence of lymphadenopathy, hepato- and splenomegaly in some patients suggested the diagnosis of acute rheumatic fever. The chief physical signs observed in this series are listed in Table V.

TABLE V. PHYSICAL FINDINGS (SEVENTY-TWO CASES)

FINDING	NO.
Fever	72
Pallor	72
Heart murmur	65
Hepatomegaly	64
Hepato + splenomegaly	54
Hemorrhagic manifestations	52
petechiae	37
ecchymoses	27
bleeding gums	19
retinal hemorrhage	6
} in combination	
Generalized adenopathy	36
Bone tenderness	6
Joint swelling	2

*Laboratory Findings.*—Sixty-nine, or 95.8 per cent, of the patients had varying degrees of anemia at the time of admission; the remainder developed anemia during the course of the disease. Hemoglobin values (Sahli) ranged from 3.0 to 10.5 Gm. per 100 c.c.; the red cell counts, from 500,000 to 3,500,000 per cubic millimeter.

Initial leucocyte counts ranged from 640 to 600,000 per cubic millimeter with twenty-three patients having a total white cell count of less than 10,000<sup>3</sup> per cubic millimeter on admission, and an additional fifteen showing a fall below 10,000 per cubic millimeter at some time during the course of the disease. Only two patients with an initial leucopenia showed a subsequent increase above 10,000<sup>3</sup> per cubic millimeter.

Peripheral platelet counts were recorded in fifty-nine patients. In fifty-three of these the counts were below 100,000<sup>3</sup> per cubic millimeter or the platelets on blood smears were reduced or absent. In forty-eight of these latter patients, signs of hemorrhage were present, the common sites being the skin, retinae, or gums. Only six patients had normal platelet counts and four of these showed bleeding tendencies. Actual leucemic involvement of the blood vessels was presumed to be responsible for the bleeding in these cases.

Bleeding times were prolonged, clotting times normal, and clot retraction delayed or absent in all recorded instances.

Abnormal leucocytes were present in the peripheral blood at some time during the course of the disease in all cases. Identification of the type of abnormal cell was often difficult, requiring subsequent sternal marrow studies and oxidase stain to validate initial identification.

Sternal marrow aspiration biopsies were employed in fifty-four patients and in all cases abnormal leucocytes were demonstrated in the marrow tissue. The marrow was hyperplastic in the majority of cases with a depression of erythropoietic tissue paralleling the peripheral anemia. Megakaryocytes were recorded as lowered or absent in all cases showing a reduction of peripheral platelets.

*Roentgenographic Changes in the Long Bones.*—The literature contains many reports of the roentgenographic changes in the long bones in childhood leucemia. Most of the reports, however, present isolated cases or small series of cases and they may have created the impression that osseous changes in the long bones in this condition are uncommon.

In the few reports of large series of cases, the incidence of osseous change has been over 50 per cent. Baty and Vogt<sup>4</sup> in 1935 demonstrated roentgenographic changes in the long bones in over 70 per cent of forty-three patients. Kalayjian, Herbut, and Erf<sup>5</sup> surveyed the literature up to 1946 and found 144 children with leucemia in whom bone changes were reported and they added two of their own cases. More recently, Landolt<sup>6</sup> demonstrated osseous changes in 75 per cent of a series of forty-eight children. In his comprehensive review of 103 children with leucemia, Silverman<sup>7</sup> found the incidence of skeletal changes to be over 50 per cent. In the present series osseous lesions were noted in 72.5 per cent of the forty infants and children in whom roentgen examinations of the long bones were available.



TABLE VI. ROENTGENOGRAPHIC CHANGES IN THE LONG BONES (FORTY CASES)

		NO.	PER CENT
<i>Cases with roentgenographic changes</i>		29	72.5
a. Transverse radiolucent band	27		93.1
b. Osteolysis	12		4.1
c. Periosteal elevation	7		2.4
<i>Cases without roentgenographic changes</i>		11	27.5

The various lesions found in the skeletal system in childhood leucemia have been described in the literature. Four main types have been reported: (1) a transverse band of diminished density in the metaphyses of the long bones immediately adjacent to the epiphyseal plate; (2) Osteolysis. (3) Periosteal elevation and new bone formation; (4) Osteosclerosis.

The lesions tend to occur in combination in individual patients but solitary bone changes may appear. The incidence and types of osseous change found in our forty patients are shown in Table VI.



Fig. 2.—Transverse bands of diminished density in the metaphyses of the distal femori and proximal tibiae in a male patient aged 8 years with acute lymphoid leucemia.

The most frequently encountered lesion was the transverse band of diminished density in the metaphyses of the long bones. This change was described first by Baty and Vogt<sup>4</sup> in 1935. In our experience the band was the first skeletal change in the majority of patients and it was the sole osseous change in thirteen of the twenty-nine patients manifesting skeletal lesions. It tended to appear in the areas of most rapid growth: the distal femora, tibiae, radii, and ulnae in decreasing order of frequency. It was not noted in areas

of slow growth such as the proximal ulnae and radii. The distribution in individual patients tended to be widespread and symmetrical. The band varied from 1 to 7 mm. in width and tended to become more clearly defined as the disease progressed. Recognition of the band in one patient thirty days following a completely negative roentgen study of the long bones demonstrates that it can appear within a relatively short period of time. One patient with a transient remission of her clinical and hematologic findings revealed a complete disappearance of the band during a period of one and one-half months. This observation suggests that this osseous change is reversible. In the early stages of the disease in several patients, the band was incomplete and extended only partially across the metaphysis. As the disease progressed, serial roentgenograms revealed complete extension across the entire width of the metaphysis. In a few cases it was difficult to distinguish between the band and osteolysis in the metaphyses. The exact nature of the process responsible for the appearance of this lesion is not clearly understood. In one patient the region of the band at autopsy was found to be occupied by hemorrhage. Erb<sup>8</sup> in 1934 found the area to be occupied by leucemic cells and considered that local pressure necrosis of the spongiosa by the proliferating leucemic cells produced the lesion shown on roentgen examination. The widespread distribution of the band in our patients and the presence of an identical band in scurvy, congenital syphilis, congenital biliary atresia, cystic fibrosis of the pancreas, in a few apparently healthy newborn infants, and in patients suffering from chronic disease associated with malnutrition suggests that non-specific interference with endochondral bone formation may play a role in its production.

Osteolysis was the next most frequently encountered lesion in the series. According to Erb,<sup>8</sup> the lesion is due to atrophy and pressure necrosis of the spongiosa and the compacta of the bone by proliferating leucemic cells. Autopsy findings in several of our cases revealed the presence of leucemic cells in areas of destruction corresponding to the areas of osteolysis seen on roentgen examination. This lesion was found in twelve patients. It never appeared as an isolated lesion but always was associated with the transverse band of diminished density or with periosteal elevation. The osteolysis was widespread and tended to be symmetrical, involving the distal rather than the proximal portions of the bones. In no case was the lesion confined to a single bone. In several patients the small tubular bones of the hands and feet were involved, and in a few patients destructive changes were noted in the iliac bones, mandible, ribs, skull, and vertebrae. The lesions varied from small, irregular areas of radiolucency localized to the shafts or metaphyses to diffuse destruction of the cortex and trabeculae, which in one case gave rise to pathologic fractures of the involved bones.

Periosteal elevation with new bone formation was the third most frequent roentgenographic change. The appearance of the lesion differed in no



Fig. 3—Diffuse osteolysis of the femur. There are no sclerotic or productive changes except for the new subperiosteal bone formation. Female patient, aged 6 years, with acute lymphoid leucemia.



Fig. 4—Periosteal elevation involving the humerus, ulna and radius. The bones also show a diffuse osteolysis. No productive changes are present. Female patient, aged 6½ years, with acute lymphoid leucemia.

respect from that recorded by Taylor,<sup>9</sup> Karelitz,<sup>10</sup> and Kalayjian, Herbut, and Erf.<sup>5</sup> The elevation tended to involve one or more of the long bones. It was noted as a linear density parallel to but separate from the shaft of the bone and either involved segments of the shaft or cloaked the bone. In all seven patients in which it appeared, the elevation was associated with osteolytic lesions. In two patients the small tubular bones of the hands and the feet were involved. The new bone tended to be deposited in a smooth, regular fashion except in two patients, in whom the deposition was rough and



Fig. 5.—Perosteal elevation and new bone formation. Male patient, aged  $4\frac{1}{2}$  years, with acute lymphoid leucemia.

irregular. Proliferating leucemic cells which had lifted the periosteum from the shaft were found in the subperiosteal area by Kalayjian, Herbut, and Erf.<sup>5</sup> Microscopically new subperiosteal bone formed from osteoblasts may be deposited parallel to or at right angles to the longitudinal axis of the shaft.

The fourth osseous change, osteosclerosis, was not noted in this series. It is usually a late change resulting from stimulation of osteoblasts and the

formation of new bone or the fibrous and osseous repair of destroyed areas within the bone. Perhaps the absence of osteosclerosis in this series is attributable to failure to obtain serial roentgenograms of the long bones of the patients as the disease progressed. In four recent cases not included in this series, sclerotic changes were noted in the long bones on serial examinations over periods of several months during the course of the disease.

No correlation between the sex of the patients and the frequency of appearance of osseous change was noted in this study. However, there was a definite relationship between the age of the patients and the incidence of skeletal lesions. Although only thirty-seven, or 51 per cent, of the seventy-two patients in the series were less than 6 years of age, twenty-one, or 72.4 per cent, of the twenty-nine patients with bone changes were under 6 years of age. Similarly, although only twenty, or 28 per cent, of the seventy-two patients in the series were less than 4 years of age, fifteen, or 51.7 per cent, of the twenty-nine patients with bone changes were under the age of 4 years.

Eighteen, or 62.5 per cent, of the patients with skeletal lesions had the acute lymphoid type of leucemia.

The incidence of osseous changes in the series increased as the duration of the disease increased. The average duration in patients with bone lesions was eight weeks while those with no demonstrable lesions averaged two weeks. Serial roentgenograms of the long bones of several patients revealed the appearance of bone changes as the disease progressed. Again it is probable that the over-all incidence of osseous lesions in this series would have been higher if serial studies had been obtained in all patients.

All twenty-nine patients with osseous changes on roentgen examination showed involvement of the knee area. The constancy of this may present the radiologist and the clinician with a simple screening measure in suspected cases of leucemia in children and obviate the necessity of more expensive and time-consuming skeletal surveys.

#### DISCUSSION

Osseous changes in childhood leucemia, although frequent, are not specific. The lesions can be produced by any primary, metastatic, or infectious condition which leads to proliferation of normal or abnormal cells in the bone marrow. Sympathicoblastomas of the adrenal gland, metastasizing to the skeletal system, may produce a picture identical to that of leucemia. Scurvy, congenital syphilis, osteomyelitis, and rickets may also produce many of the changes encountered in leucemia. Conditions which interfere with the normal sequence of endochondral bone formation may produce the transverse band of diminished density. The presence of the described osseous lesions in a child, especially if associated with unexplained fever, hemorrhagic tendencies, pallor, bone and joint pain, should nevertheless alert the clinician to the possibility of leucemia and lead to a complete hematologic investigation.

Leucemia in childhood often is mistaken for rheumatic fever in its early stages. Smith<sup>11</sup> called attention in 1933 to a patient with leucemia in whom the complaint of bone and joint pain and the finding of joint swelling suggested the diagnosis of acute rheumatic fever. Peripheral blood studies did not sug-

gest leucemia. Failure to respond to salicylates and a favorable response to transfusion led to doubt of the initial diagnosis. Roentgen studies of the long bones revealed the changes commonly associated with leucemia. Further investigation, including lymph node biopsy, established the diagnosis. In this series, the complaint of bone and joint pain, the presence of fever, and a systolic heart murmur in the absence of hepato- and splenomegaly led to the initial diagnosis of rheumatic fever in two patients. Roentgen examination of the long bones in both patients revealed changes consistent with leucemia. Further studies, including sternal marrow aspiration biopsy, proved the diagnosis of leucemia.

Cooke<sup>12</sup> called attention to the frequency of bone pain in childhood leucemia. This symptom is thought to be due to increased intraosseous tension secondary to the proliferation of the leucemic cells. Seventeen patients in this series manifested varying degrees of bone pain, and the fourteen who had available roentgenograms of the long bones all showed osseous changes. In addition, sternal marrow studies revealed the presence of abnormal leucocytes in each of these fourteen patients.

Although roentgen examination of the skeletal system is of value in suggesting the diagnosis of leucemia in childhood, it is not as reliable or as sensitive as sternal marrow aspiration. According to Erb,<sup>8</sup> leucemic cells were seen proliferating throughout the bone marrow in the early stages of the disease and yet the roentgenograms revealed no evidence of osseous change. In several of our cases similar findings were noted. Sternal marrow aspiration was employed in fifty-four cases of this series. In all, abnormal cells were demonstrated. In this group osseous changes were found in only 72.5 per cent of forty patients who had roentgenograms.

We believe that both roentgen examination of the long bones and sternal marrow biopsy should be employed to demonstrate abnormal cellular activity in the bone marrow in all suspected cases of leucemia. Examination of the knee area affords a simple, painless, and inexpensive screening method for detection of osseous changes and is a desirable procedure in office practice, outpatient departments, and in situations where sternal marrow aspirations are impractical. Complete skeletal surveys may be obtained in doubtful cases and serial studies of the knee area may prove of value in the detection of lesions suggestive of leucemia. The roentgen examination is also of value in differentiating leucemia from other conditions such as osteomyelitis, rheumatic fever, and rheumatoid arthritis, conditions which may simulate leucemia in its early stages. The presence of bone lesions of the types described in children with fever, pallor, bone pain, and hemorrhagic tendencies demands a thorough hematologic investigation.

#### SUMMARY AND CONCLUSIONS

1. An analysis of the clinical and roentgenographic findings in seventy-two children with leucemia has been presented.
2. Roentgen examination of the skeletal system is a valuable aid in diagnosis. It is not as specific or reliable as sternal marrow aspiration but aids

materially in the detection of osseous changes suggestive of abnormal marrow activity and points to the necessity for a thorough hematologic study of the patient.

3. Roentgen examination of the knee area provides a helpful screening technique in the investigation of all suspected cases of leucemia.

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## INTRAVENOUS PROCAINE IN CHILDREN

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**M**ANY reports have appeared recently on the use of intravenous procaine, but none of these has discussed its use in children.

Intravenous procaine was given to five children with serum sickness or a related allergic disorder and to one child with a severe burn of 60 to 70 per cent of the body surface. Symptomatic relief in patients with otherwise uncontrolled reactions has been gratifying.

### CASE REPORTS

**CASE 1.\***—N. B., a 5-year-old white boy, received 40,000 units of diphtheria antitoxin on Feb. 4, 1947. Twelve days later, on February 16, he began to complain of generalized itching and his temperature was 101° F. rectally. He had urticaria of his arms, legs, neck, face, and back. He was started on 25 mg. of Pyribenzamine three times a day. On the following day his urticaria had disappeared and he felt fine until late afternoon when he complained several times of slight difficulty in swallowing. On February 20, four days after his initial urticaria, he developed anorexia; his temperature was 100.6° F. rectally and he complained of pain and tightness of his throat. By 7 P.M. he again had generalized urticaria. He was unable to move his legs and had severe muscle and joint pains. Pyribenzamine was stopped at this time.

On Feb. 21, 1947, he was admitted to the hospital where examination revealed an acutely ill boy with a temperature of 101.8° F. rectally and a pulse rate of 138 per minute. He had severe generalized urticaria. He had extreme myalgia and arthralgia and cried from pain elicited by light palpation of the muscles of his lower extremities. There was slight edema of the knee and ankle joints. Flexion of the knees was limited by pain to about 25 degrees. There was some abdominal distention, and he had generalized small, firm, non-tender, lymph nodes.

Complete blood count was normal except for a total leucocyte count of 12,800 with a normal differential. There was no eosinophilia. Urinalysis was negative. Conjunctival and intradermal tests with 0.1 per cent procaine hydrochloride solution were negative. The urticarial wheals faded for an area of 6 cm. in diameter around the site of the intradermal injection.

About twenty minutes after the completion of the physical examination he was given 0.25 Gm. of procaine hydrochloride diluted with 250 c.c. of isotonic solution of sodium chloride. This solution was given intravenously by the gravity drip method at a rate of approximately twenty drops per minute. At the end of one hour when about one-half of the solution had run in, the patient felt fine, the urticaria had decreased approximately 75 per cent, and he was able to move his legs freely. He still had slight pain in his knee joints on flexion. By the end of the second hour the administration of intravenous procaine was complete and he was asymptomatic except for a very faint annular urticaria of his elbows and knees. His temperature was normal

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\*Patient of Dr. David Greer, treated at St. Joseph's Infirmary, Houston, Texas.



and his pulse rate was 120 per minute. The following day he received three injections of adrenaline in oil and 50 mg. of Pyribenzamine every six hours for three doses because of some recurrence of urticaria. There was no recurrence of muscle or joint pain or edema.

He made a rapid recovery and remained well during the following nine months of observation.

CASE 2.\*—M. L., a 5-year-old girl, was admitted to the hospital on March 3, 1947, with a temperature of 100.4° F. rectally, slight swelling, redness, and heat of all large joints, and generalized circinate urticaria.

Complete blood count was normal and urine was negative except for a trace of albumin.

She was given 0.2 Gm. of procaine hydrochloride in 125 c.c. of isotonic saline solution over a two-hour period. All joint manifestations and urticaria had disappeared before completion of the infusion.

She was discharged the following day completely recovered except for a few small areas of urticaria on her extremities.

No cause for this patient's allergic reaction could be elicited by history.

CASE 3.†—C. S., a 4½-year-old boy, was admitted to the hospital on July 11, 1947, with a six-day history of pain in right hip and knee, and transient urticaria. Pain on the day of admission was severe and he had not been relieved by adequate doses of "antihistaminics."

Physical examination was not remarkable except for generalized urticaria and severe pain in his right hip and knee on movement. Complete blood count was normal and the urine was negative.

He was given 0.5 Gm. of procaine in 250 c.c. of physiologic saline solution over a period of fifty minutes and received immediate and permanent relief from pain. During the administration he became restless, irritable, and finally very jumpy. He was given 64 mg. of Sodium Amytal intravenously and symptoms of central nervous system stimulation ceased.

No definite explanation of his illness could be elicited by history.

CASE 4.—J. S., an 11-year-old white boy, was given an injection of tetanus antitoxin (unknown amount) by his local physician on July 4, 1947. He had had one other injection of tetanus antitoxin about three years prior to the present one. There was a familial history of allergy.

On July 10, six days after receiving the tetanus antitoxin, he developed "hives." On July 11 he had aching and swelling of his fingers and knees. Physical examination revealed an acutely ill boy with generalized urticaria and painful and swollen interphalangeal and knee joints. He was given ephedrine sulfate, then adrenaline chloride intramuscularly and finally calcium gluconate intravenously. He received moderate relief for only one hour.

He was sent to the hospital on July 11, 1947, where physical examination revealed an acutely ill boy in severe pain. His temperature was 99.2° F. rectally and pulse rate was 90 per minute. He had generalized urticaria, swollen lips, tongue, and eyelids, and edema of his interphalangeal and knee joints.

Complete blood count was normal except for a white blood cell count of 14,100 with 87 per cent neutrophils. Urine was negative except for a faint trace of albumin and four plus acetone.

He was given three minims of adrenaline chloride, five minims of adrenaline in oil, and 50 mg. of Benadryl with only slight relief from symptoms. He then developed severe pain in his left hip and edema of his left ankle.

\*Patient of Dr. David Greer, treated at St. Joseph's Infirmary, Houston, Texas.

†Patients of Dr. Byron York, treated by Dr. George Salmon at St. Joseph's Infirmary, Houston, Texas (Cases 3 & 4).

At 1:30 P.M., the intradermal test with 0.1 per cent procaine solution was read as negative. Five hundred cubic centimeters of isotonic solution of sodium chloride containing one gram of procaine was started by slow intravenous drip. Only 150 c.c. of the solution had run in at the end of thirty minutes, but the patient had complete relief of all itching and joint pain and partial relief of the edema of his hands and left ankle. The rate of administration was increased and the remainder of the solution was given in only thirty minutes without reaction. The patient had complete relief from itching and pain for five or six hours.

By the next morning, however, the patient had severe pain in his right hip and he was again given intravenously 500 c.c. of isotonic solution of saline containing one gram of procaine hydrochloride over a period of one and one-half hours. He received complete relief from his hip pain but developed slight pain in his right ankle. The following day he was suffering from excruciating pain in both hips and the administration of intravenous procaine was repeated with partial relief from pain. This time the solution was administered at a fairly rapid rate over a period of only one hour and the patient complained of headache, dizziness, and nausea.

After the last administration of intravenous procaine on July 13, 1947, the symptoms of serum sickness gradually subsided and he was discharged from the hospital July 15, 1947, completely recovered. He has had no recurrence.

CASE 5.—W. B., a 4½-year-old boy, entered the North Carolina Baptist Hospital on May 18, 1948. Four weeks prior to entry he was given sulfadiazine by his local physician for acute tonsillitis. Two weeks prior to entry he was started on 50,000 unit tablets of penicillin and received his last dose nine days before entry. Three days before entry he ate fresh strawberries, to which he was accustomed. Forty-eight hours before entry he developed generalized urticaria, then swollen, red, stiff, painful, toes and fingers, followed by generalized edema of hands, feet, and ankles, and "marble-sized knots" on his scalp. During the forty-eight hours before entry he vomited repeatedly and became delirious and unmanageable. One local physician gave him three injections of adrenaline with only partial relief for three to four hours and another physician gave him 50 mg. of Benadryl every two hours for the twenty hours just prior to entry with little or no relief.

Past history revealed that he had received penicillin about two years prior to entry without reaction and had taken sulfonamides on several occasions without reaction. Family history was negative except that one aunt has had hay fever, hives, and asthma.

Physical examination on entry revealed an acutely ill, irritable, semi-delirious boy with generalized fiery red, circinate, raised urticarial lesions, generalized small, tender lymph nodes, edema of eyelids, hands, feet, and ankles, and inability to walk because of pain. His temperature was 102 ° F. rectally; pulse 138 per minute; respirations 28 per minute; blood pressure 108/68. Complete blood count was normal except for a white blood cell count of 11,350 with 87 per cent neutrophils, of which 40 per cent were nonsegmented. Urinalysis after intravenous fluids was negative except for a trace of albumin and a trace of acetone. He was skin tested with procaine, given 48 mg. of sodium phenobarbital intramuscularly, and after thirty minutes a continuous drip of 250 c.c. of physiologic saline solution containing 250 mg. of procaine hydrochloride was started. By the end of forty-five minutes he was very restless and 32 mg. of sodium phenobarbital were given intramuscularly. By the end of one hour he was sleeping soundly and about 40 per cent of the urticaria

had disappeared. By the end of two hours all of the solution had been administered; the urticaria had decreased only about 40 per cent but he was still sleeping soundly. He had not slept for forty-eight hours prior to this, and after intravenous procaine he slept for ten hours, waking only two times for short periods. The next morning the urticaria had decreased by about 60 per cent but he still had some edema of his face, hands, and feet. During the following eight hours he continued to improve and was started on 50 mg. of Pyribenzamine every four hours and discharged after forty hours with only faint scattered urticaria and slight edema of his hands and feet. He was kept on decreasing doses of Pyribenzamine for one week.

CASE 6.\*—J. L., a 3-year-old girl, was admitted to the emergency room of the North Carolina Baptist Hospital March 24, 1948, with a severe burn estimated by the surgical department as being 60 to 70 per cent of the body surface. Superficial débridement and a cut down were done under drop ether anesthesia. After recovering from anesthesia she was in severe pain and became unmanageable. Two hundred fifty cubic centimeters of 2.5 per cent glucose in 0.5 normal saline containing 250 mg. of procaine were started by slow drip in the cut down and given over a period of one and one-half hours. She was fairly quiet during the administration and for about five hours after completion of the infusion. No further intravenous procaine was given because of her need for plasma and other fluids. This patient has had no adverse reactions during six months of observation.

#### COMMENT

The proper dosage of intravenous procaine has not been determined. Allen<sup>1</sup> has used large doses in obstetrics and in surgical procedures with very little difficulty. For the relief of postoperative pain, he gave one patient two grains of sodium phenobarbital intramuscularly and followed this with an intravenous infusion of 10 Gm. of procaine hydrochloride in 800 c.c. of 5 per cent glucose in distilled water. This solution was given at an average rate of 3 c.c. per minute. When the rate of administration was speeded up to 8 c.c. per minute the patient complained of dizziness.

The number of injections of intravenous procaine that a patient can tolerate has not been determined. Allen<sup>2</sup> gave one patient twenty-five intravenous infusions of procaine in forty days for the relief of severe anginal attacks. This patient had no apparent injurious effects. There have been few animal experiments on this problem.

The length of effect of procaine is not known. Gordon<sup>3</sup> found that pain associated with burns was abolished for from six to twelve hours after the administration of the intravenous procaine. The fourth patient we treated received relief from pain and itching for from four to eight hours after the completion of the procaine infusion. Since procaine is hydrolyzed and detoxified by procainase in the blood stream a few minutes after injection,<sup>4</sup> it is difficult to explain the relief of pain for hours. The role of the breakdown products of procaine has not been determined.

State and Waugensteen<sup>5</sup> suggested several explanations for the action of procaine: namely, the direct action on cells, antiacetylcholine action, epinephrine potentiating action, and a possible antihistamine effect. The formulas

\*Private patient of Dr. Felda Hightower, Department of Surgery, Bowman Gray School of Medicine, Winston-Salem, N. C.

for Benadryl, Pyribenzamine, and procaine are closely related structurally. All three drugs contain either an aminoethyl or an ethylene diamine group and procaine breaks down into diethylaminoethanol and para-aminobenzoic acid. Both Pyribenzamine and Benadryl counteract the spasmogenic effect of acetylcholine and all three drugs relieve phases of serum sickness. Benadryl and Pyribenzamine are effective in over 80 per cent of the cases of serum sickness in the relief of skin lesions such as urticaria.<sup>6</sup> Patients with joint involvement are not usually helped,<sup>6</sup> however, and intravenous procaine may be of value.

Early toxic symptoms observed in the use of intravenous procaine are numbness, nausea, and dizziness. If any of these symptoms develops, the rate of administration should be decreased. If further evidences of toxicity such as restlessness and irritability appear, the drip should be discontinued and sodium phenobarbital should be given intramuscularly. Convulsions and respiratory failure have been attributed to the local use of procaine but have not been encountered in slow intravenous drip administration. Intravenous Sodium Amytal may be given to control convulsions and artificial respiration administered in the event of respiratory depression. One author<sup>4</sup> has reported the use of intravenous procaine in 2,000 patients without ill effect.

Procaine probably should not be administered to patients (1) who are hypersensitive by skin test, (2) who have extensive liver damage, (3) who suffer from myasthenia gravis, (4) who have epilepsy or family history of epilepsy, or (5) who have a history of recent head injury.<sup>7</sup> Procaine is probably not contraindicated in patients receiving sulfonamides.<sup>8</sup>

#### SUGGESTED TREATMENT SCHEDULE

General factors of dosage which should be considered in the administration of intravenous procaine are: concentration of procaine, quantity of fluid, rate of administration, and duration of administration. An arbitrary dosage schedule and procedure for children have been devised:

1. Skin test with 0.1 per cent procaine hydrochloride.
2. Appropriate dosage of phenobarbital twenty minutes before start of intravenous procaine.
3. Procaine hydrochloride dissolved in either physiologic saline or 5 per cent glucose in water so as to give a 0.1 per cent solution.
4. Intravenous administration by slow drip (twenty to thirty drops per minute) over a period of at least two hours.
5. Repeat in eight hours if necessary.
6. Have on hand Sodium Amytal for intravenous use in case of excessive central nervous system stimulation.
7. Amount of fluid according to age:
  - 2 to 5 years—125 to 250 c.c. of 0.1 per cent procaine solution.
  - 5 to 10 years—250 to 500 c.c. of 0.1 per cent procaine solution.
  - 10 to 15 years—500 to 750 c.c. of 0.1 per cent procaine solution.

## SUMMARY AND CONCLUSIONS

Six children were given intravenous procaine for the relief of symptoms. Five had serum sickness or a related allergic disorder and one was suffering extreme pain from an extensive burn. A treatment schedule for children is presented.

Patients who have severe manifestations of serum sickness such as myalgia and arthralgia and who are not relieved by the so-called "antihistaminics" may benefit from the use of intravenous procaine. Patients with other painful conditions, particularly those with capillary damage as in extensive burns, may receive symptomatic relief.

I wish to express my appreciation to Drs. David Greer, Byron York, and George Salmon of Houston, Texas, and Dr. Felda Hightower of Winston-Salem, N. C., for permission to include case histories of their patients in this paper.

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## METHYL TESTOSTERONE IN THE TREATMENT OF PREMATURE INFANTS

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A PRELIMINARY report by Shelton and Varden<sup>1</sup> suggested that the administration of testosterone preparations to premature infants was of value in decreasing the expected mortality rate of infants weighing less than 2,000 Gm. at birth and that, by promoting a more satisfactory weight curve, it decreased the period of hospitalization necessary for each infant. A subsequent more complete report<sup>2</sup> tends to confirm these impressions. No untoward effects of the drug were noted by the authors.

It is generally accepted that the administration of methyl testosterone to an individual brings about an increase in nitrogen retention, protein anabolism, and tissue growth.<sup>3</sup> Therefore, it seems reasonable to hope that the administration of this substance to premature infants might be of value in promoting growth as measured by gain in body weight.

An effort to determine if testosterone is of practical value in this respect was made between May and November of 1947 in the Nursery Unit for Premature Infants in the Harriet Lane Home, The Johns Hopkins Hospital. Alternate premature infants were given methyl testosterone by mouth twice daily, 2.5 mg. emulsified in 5 c.c. of sterile water and given by medicine dropper or gavage tube immediately before feeding. In all except two patients the treatment was begun on the seventh to tenth day of life. In patient A (Chart 1) it was begun at 11 weeks and in patient H at 6 weeks. The medication was continued for four weeks. In most instances it was withdrawn abruptly, but in some the dose was reduced to 2.5 mg. daily for an additional three days and then discontinued.

The infants receiving methyl testosterone and those serving as controls were all handled according to the standard nursery regime. Feedings consisted of half-skimmed milk with 10 per cent added carbohydrate, having a caloric value of one calorie per cubic centimeter of formula. After the tenth day of life 120 to 130 calories per kilogram of body weight were fed daily. Supplementary vitamins A, C, and D were started on the fifth or sixth day of life.

In all, twenty-six infants, varying from approximately 900 to 1,900 Gm. at birth, were given methyl testosterone as described above. Their response to therapy as measured by computing the average daily weight gain for the total period of hospitalization (including the period of initial weight loss) was compared with that of the control, untreated group. The results of this comparison may be seen in Table I. In order that a graphic representation might be made, a group of infants of varying birth weight was chosen from the testosterone-

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treated group and paired off with an untreated infant of the same sex and race, of approximately the same birth weight. The selection was done by an individual who had no knowledge of the clinical course of the infants in either group.

In addition, six infants weighing between 850 and 1,370 Gm. at birth were each given 4 mg. testosterone propionate in oil intramuscularly, on the first day of life and every third day thereafter. All six died between the second and tenth days of life and are not included in this study.

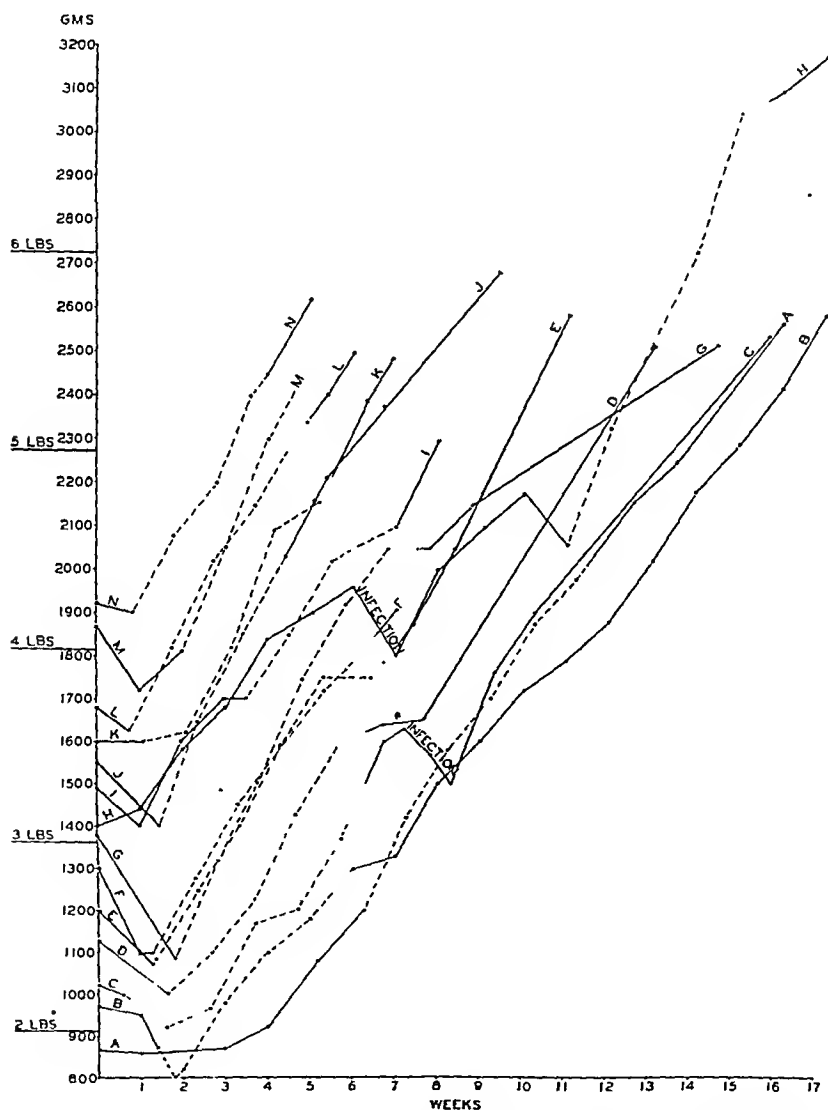


Chart 1—Weight curves of premature infants receiving methyl testosterone 2.5 mg. twice daily given during the period marked by broken line; 2.5 mg. once daily during the period marked by dotted line. No therapy during period marked by solid line.

TABLE I

BIRTH WEIGHT (GM.)	NO.	2.5 MG. METHYL TESTOSTERONE TWICE DAILY (AVERAGE DAILY GAIN IN GM.)	NO.	CONTROL (AVERAGE DAILY GAIN IN GM.)
800- 990	2	15.5	2	15.6
1,000-1,199	5	16.3	5	17.3
1,200-1,399	4	15.7	6	17.6
1,400-1,599	6	17.4	4	16.5
1,600-1,799	5	17.9	3	19.5
1,800-1,999	2	21.7	6	20.6
2,000-2,199	2	15.1	0	
Totals	26	17.0	26	18.2

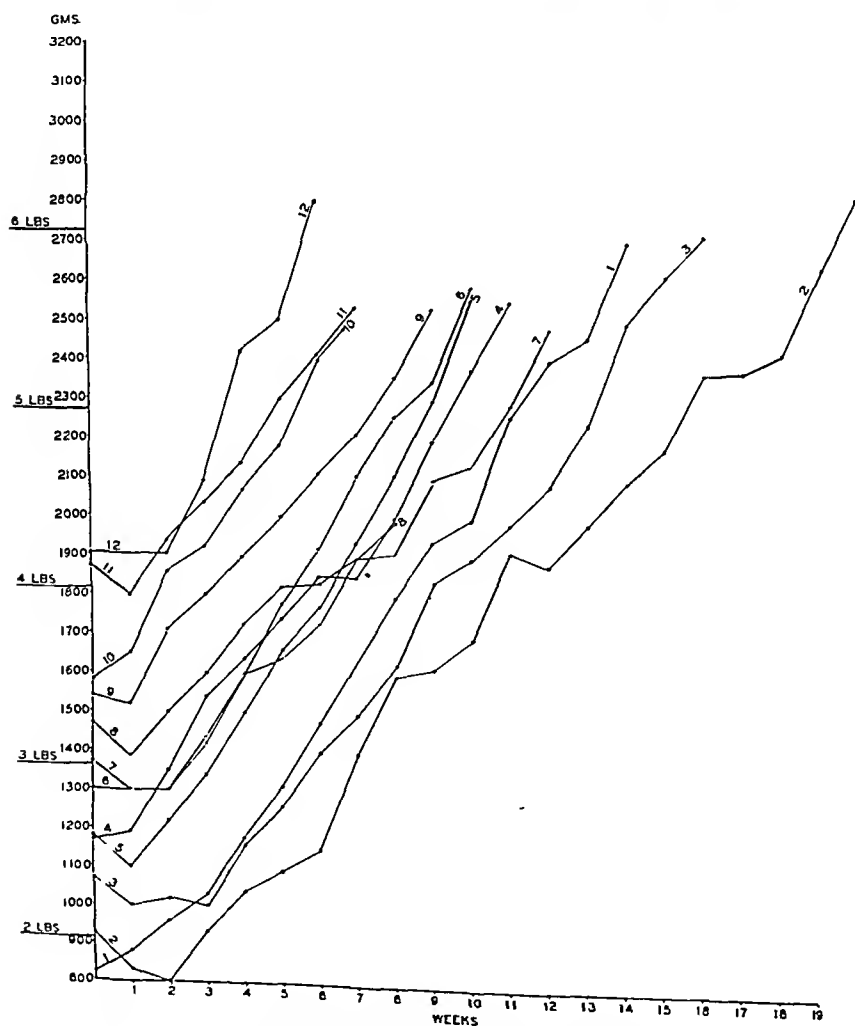


Chart 2.—Weight curves of premature infants raised on same general regime as those in Chart 1 but given no testosterone.



## RESULTS

As may be seen by comparison of the graphic charts, there is no significant difference in the weight curves of the infants treated with methyl testosterone and those who did not receive the drug. Furthermore, as shown in Table I, the average daily weight gain of 17 Gm. made by the infants treated with testosterone is not significantly different from an average daily weight gain of 18.2 Gm. in the control group.

The only child in whom any dramatic effect was observed was patient H (Chart 1), who did not receive the drug until he was 10 weeks of age. This was a twin who had failed to gain at the expected rate. He gained rapidly during the period of treatment but continued to do so after the drug was withdrawn.

No untoward effects of the medication were noted. Two of the male infants showed moderate enlargement of the penis, which has persisted. Several of the girls showed transient enlargement of the clitoris.

It is of interest that in very few instances was weight loss observed at the termination of the testosterone therapy, whereas in older patients having increased protein anabolism with testosterone, a transient loss of weight and nitrogen usually occurs on its withdrawal. This suggests that the drug had had no marked effect in increasing nitrogen retention.

## CONCLUSION

In the clinical experiment described above, no benefit was observed from the use of methyl testosterone in the treatment of premature infants.

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# CARBOHYDRATE SUPPLEMENTS (LACTOSE AND STARCH HYDROLYSATES) IN INFANT FEEDING

## BLOOD SUGAR CHANGES FOLLOWING THE ADMINISTRATION OF CARBOHYDRATE SUPPLEMENTS IN VARIOUS MILK MEDIA

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THESE studies were initiated in an attempt to evaluate carbohydrate supplements in infant feeding for the neonatal period by the classical, statistical approach. Our failure to obtain convincing results by this method in 1,227 cases led us to use blood sugar tolerance curves for this purpose. By the latter method it was found that the addition of lactose to heated milk formulas produced, in the infant, sugar tolerance curves different from those obtained by feeding lactose in raw milk formulas.

The high carbohydrate requirement of infants has been emphasized by Heymann.<sup>1</sup> He pointed out that in infants hypoglycemia is easily induced by carbohydrate starvation, the glycogen reserves of the liver are low, and the carbohydrates are of importance in water retention. It also has been said by Winter<sup>2</sup> that the normal fasting blood sugar levels are low in infants, probably due to the poor ability to absorb foods in general.

The lack of agreement in the literature on studies where growth curves were used as a criterion of the nutritional value of a carbohydrate led us to question this as a sole method of evaluating a feeding formula. The number of cases used in many of these studies seemed to us, merely from a cursory inspection, to be too small to warrant the conclusions drawn. This objection could be met in one of two ways. One method would be to carry out the study on large numbers of carefully controlled cases. The other alternative would mean the setting up of our experiments in such a way that a specific biologic effect would be studied.

We decided to test the first method by finding out how many cases would be necessary to establish average growth curves on basic hospital formulas. The basic formula used in this hospital consists of one part evaporated milk, two parts sterile water, and 5 per cent added carbohydrate. Both Cartose\* and Dextri-Maltose† were used as the added carbohydrate in this study. Breast-fed infants who, in addition, received basic Cartose and Dextri-Maltose formulas "post cibum" also were studied. Growth curves were drawn for each infant for the first seven days of life. This arbitrary period was necessarily chosen since many infants left the hospital after the seventh day.

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Read by title at the Proceedings of the Federation of American Societies for Experimental Biology in March, 1948, Fed. Proc. 1: 175, 1948.

\*Cartose is manufactured by the Winthrop-Stearns Co.

†Dextri-maltose is manufactured by Mead Johnson and Co.

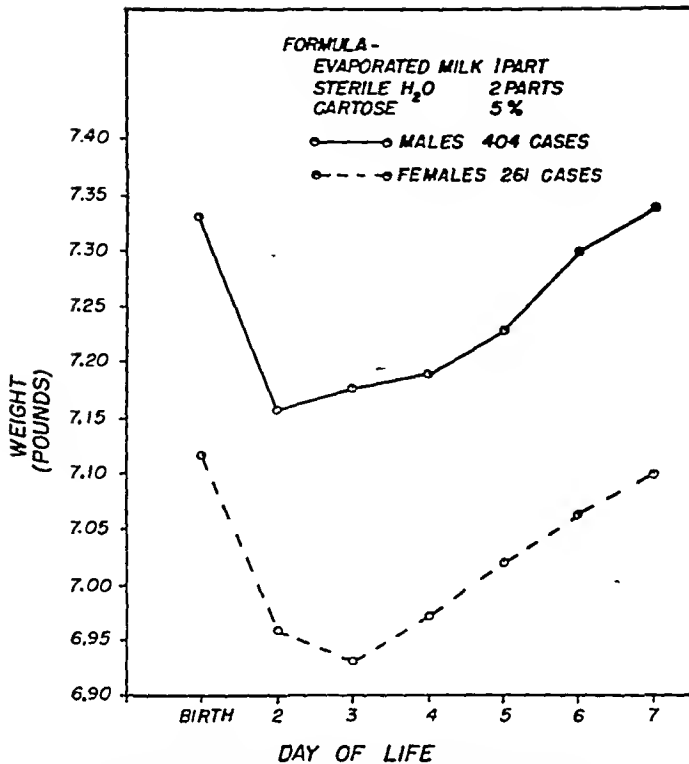


Fig. 1.—Average curve for the weight change of normal infants during the first seven days of life on evaporated milk formula plus Cartose.

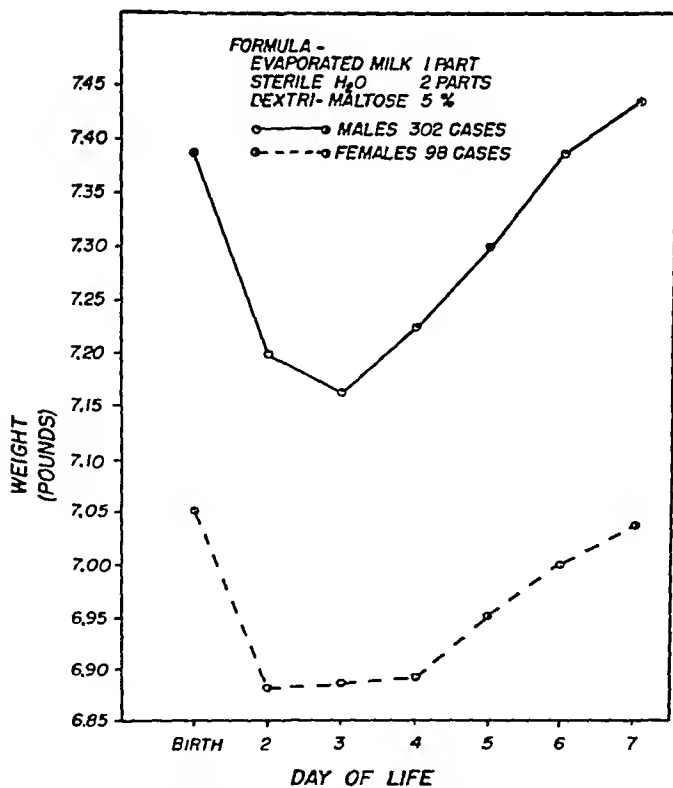


Fig. 2.—Average curve for the weight change of normal infants during the first seven days of life on evaporated milk formula plus Dextri-Maltose.

TABLE I. NET DIFFERENCE BETWEEN BIRTH WEIGHT AND WEIGHT AT SEVEN DAYS IN RELATION TO THE TYPE OF FEEDING

FORMULA	SEX	NO. CASES	AVERAGE BIRTH WEIGHT (LB.)	AVERAGE WEIGHT AT 7 DAYS (LB.)	NET CHANGE (%)
Evaporated milk with 5 per cent Cartose	M	404	7.33	7.36	+0.41
	F	261	7.12	7.10	-0.28
Evaporated milk with 5 per cent Dextri-Maltose	M	302	7.39	7.44	+0.68
	F	98	7.05	7.04	-0.14
Breast milk with Cartose formula or Dextri-Maltose formula "postcubum"	M	86	7.34	7.34	0.00
	F	76	7.17	7.12	-0.70

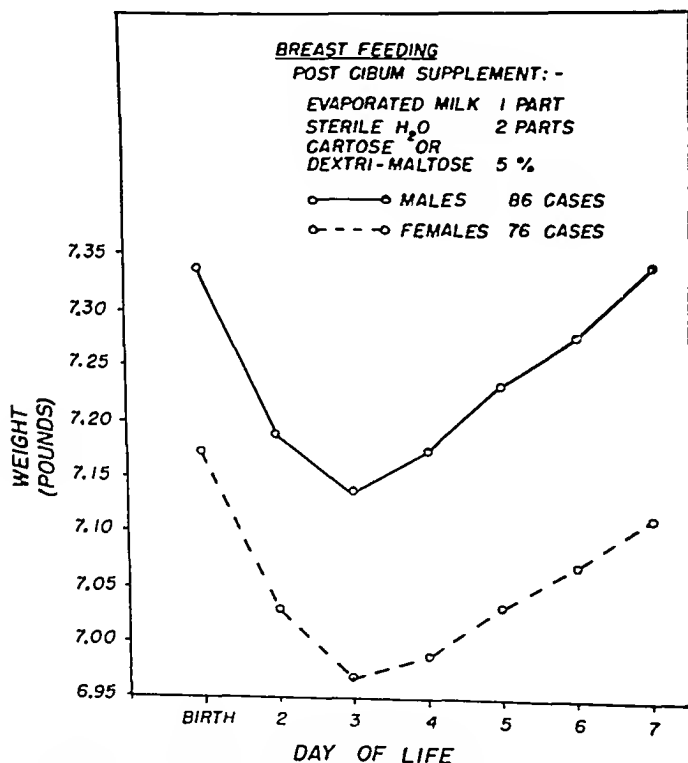


Fig. 3.—Average curve for the weight change of normal infants during the first seven days of life on breast feeding supplemented with evaporated milk formula plus starch hydrolysate.

For each formula group the daily weights were tabulated and averaged. Each point on the accompanying graphs (Figs. 1, 2, and 3), therefore, represents the average weight of all infants in a particular group on the day under consideration.

Table I expresses the net change in weight at the end of seven days as a percentage of the birth weight in a total of 1,227 infants.

Having found the statistical weight curve method tedious, depending upon the reliability of a large number of nurses, and time-consuming, with a

minimum of results, we decided to attempt a more objective method. For preliminary investigation it was decided to use the blood sugar tolerance curve.

The procedure used in the tolerance tests was as follows: The blood used was capillary blood taken from the infant's heel by needle prick. The fasting specimen was drawn at least three and one-half hours after the preceding feeding. Subsequent specimens were drawn thirty, sixty, and one hundred twenty minutes after completion of the test feeding. The bloods were analyzed for sugar content by a modification of the Folin-Wu method<sup>3</sup> further modified by us to employ 0.02 ml. of whole blood measured in a Sahli hemoglobinometer pipette, and the final color read by the Klett-Summerson photoelectric colorimeter.

The infants used in this study were normal, full-term infants born on the general obstetrical service of our hospital. All the infants were housed in the same nursery and received the same nursing care. Only healthy infants who weighed at least 5 pounds 10 ounces, but not more than 8 pounds were chosen for this study. The routine used in feeding in our hospital is as follows: Immediately after birth the infant is brought to the nursery, washed, and weighed. No liquid is given by mouth for the first eight hours of life. At the end of this eight-hour period, one-half ounce of glucose solution is given by mouth. Four hours after this one-half ounce of the stock hospital formula is given, and every four hours subsequently the infant is fed one-half ounce per feeding on the first day, and the amount is increased by one-half ounce on each succeeding day; that is, one ounce on the second day, 1½ ounces on the third day, 2 ounces on the fourth day, etc., until a maximum of 3 ounces per feeding is reached. In all of the following studies, the "first test day" is the third day of life and the "second test day" is the fourth day of life.

The formula used was the stock hospital formula with 5 per cent of the carbohydrate to be tested added. The volume administered at each test period was 2.0 ounces. The formulas were analyzed after being made up so that the carbohydrate content was the same in all.

In order to limit the number of determinations to a reasonable quantity and at the same time have our results be significant, we ran a series of studies for two successive days, comparing the reproducibility of the sugar tolerance curve in the same infant. The formula used was the stock hospital formula with 5 per cent added Cartose.\* The results are shown in the average curves in Fig. 4.

It is evident from the foregoing results that the average glucose tolerance curves of the same infants on the third and fourth days of life showed enough similarity to justify a comparative study based on this criterion.

\*The carbohydrate chosen for this study was Cartose. It is a sterile, easily soluble sugar which contains no salt or other added ingredients which might interfere with the study. Cartose is a pale amber syrup containing 77 per cent solids. One ounce by volume of the liquid is approximately equal to one ounce by weight of a powdered carbohydrate. One liquid ounce or two tablespoonfuls is equivalent to 120 calories. This would be equivalent to four tablespoonfuls of a powdered carbohydrate. Cartose is an hydrolysate of corn starch and contains no added sugar. Unlike Karo, the hydrolysis is controlled to produce a higher percentage of dextrins and maltose. Cartose is composed of approximately 36 per cent dextrins, 20 per cent malto-dextrins, 21 per cent maltose, and 23 per cent glucose. It has been found by Krost<sup>4</sup> to be a perfectly safe and well-utilized carbohydrate.

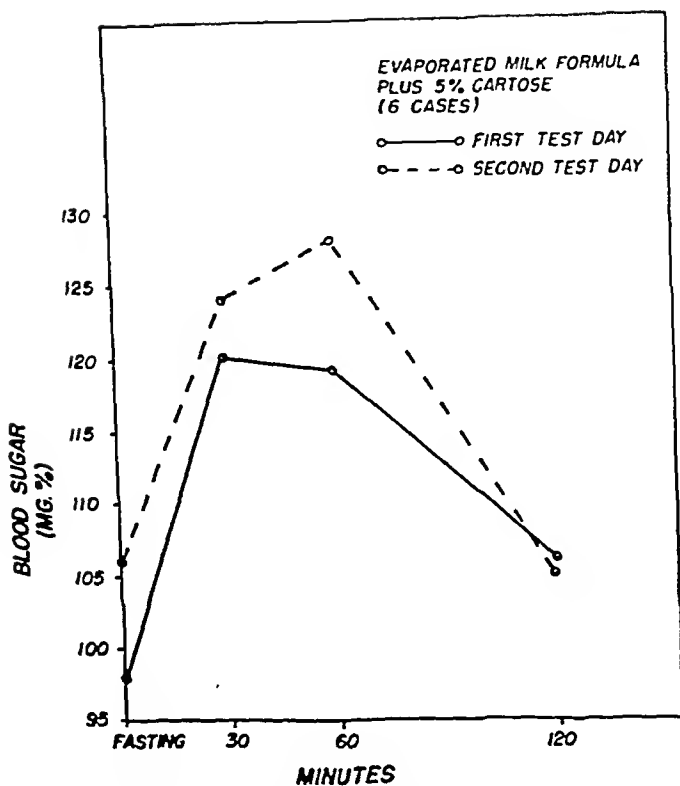


Fig. 4.—Reproducibility of average blood sugar tolerance curves on the same normal infants on succeeding days.

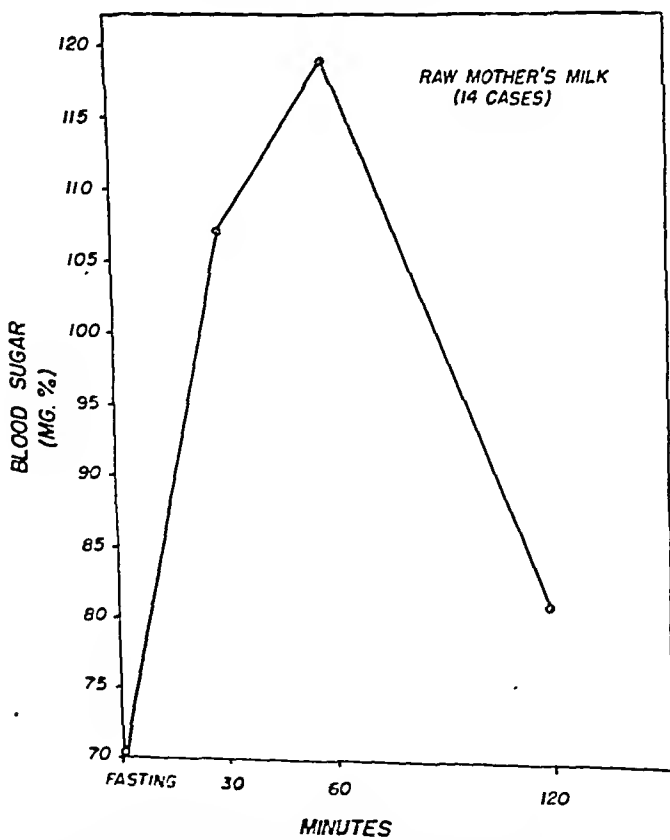


Fig. 5.—Average blood sugar tolerance curve for normal infants on raw mother's milk (approximately 7 per cent lactose content).

Lactose had been reported as producing tolerance curves with low peaks as compared to starch hydrolysates.<sup>5</sup> We, therefore, examined the blood sugar tolerance curves of fourteen infants using 2.0 ounces of raw mother's milk fed by bottle.\* This milk contained approximately 7 per cent lactose. In this study we obtained curves with high peaks which returned almost to the fasting level within two hours in each case. The average curve for these cases is shown in Fig. 5.

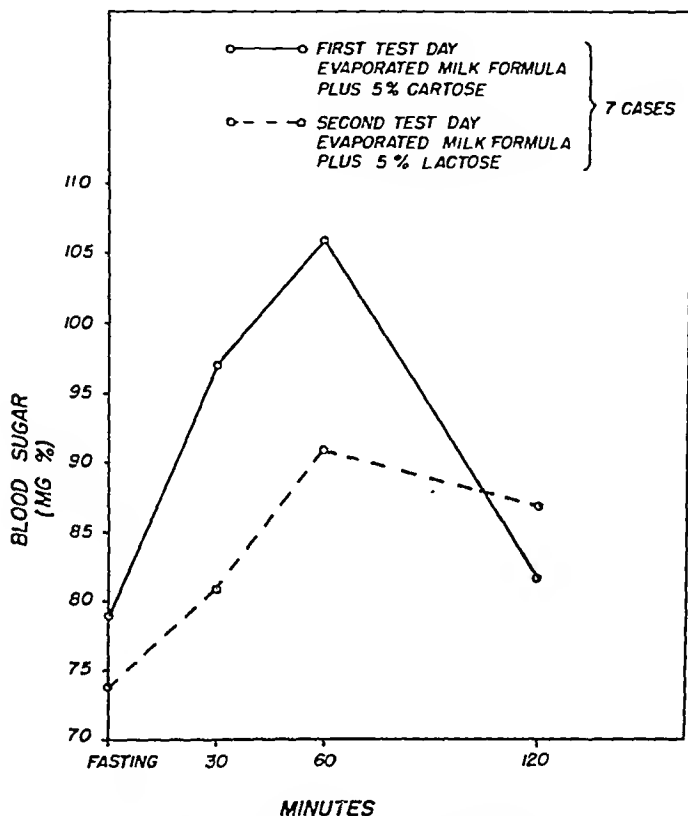


Fig. 6.—Comparison of average blood sugar tolerance curves for normal infants on starch hydrolysate and lactose administered in evaporated milk formula.

Experiments reported in the literature had been performed by dissolving the lactose in water. We considered the possibility that these experiments might not apply to milk formulas, for the medium in which the lactose was administered might have some bearing on the results obtained. To test this factor we ran a study using evaporated milk formulas on both test days, but using a 5 per cent Cartose supplement on the first test day and a 5 per cent lactose supplement on the second test day on the same infant. Fig. 6 shows the results on seven infants tested in this way.

\*Raw mother's milk was obtained from the Mothers' Milk Bureau of the Children's Welfare Federation of New York City.

Our results confirmed the fact that lactose produces curves with lower peaks which do not return to the fasting level in two hours when employed in the blood sugar tolerance test. Nevertheless, mother's milk containing 7 per cent lactose had produced tolerance curves with high peaks which had returned to almost the fasting level at the end of two hours.

Obviously, there was a distinction between evaporated cow's milk and mother's milk in influencing the shape of the sugar tolerance curve. We felt that this difference might be in the different treatments to which the milks had been subjected, rather than the species of milk used. We decided to compare the tolerance curves produced by lactose in raw cow's milk with those produced by lactose in evaporated cow's milk.

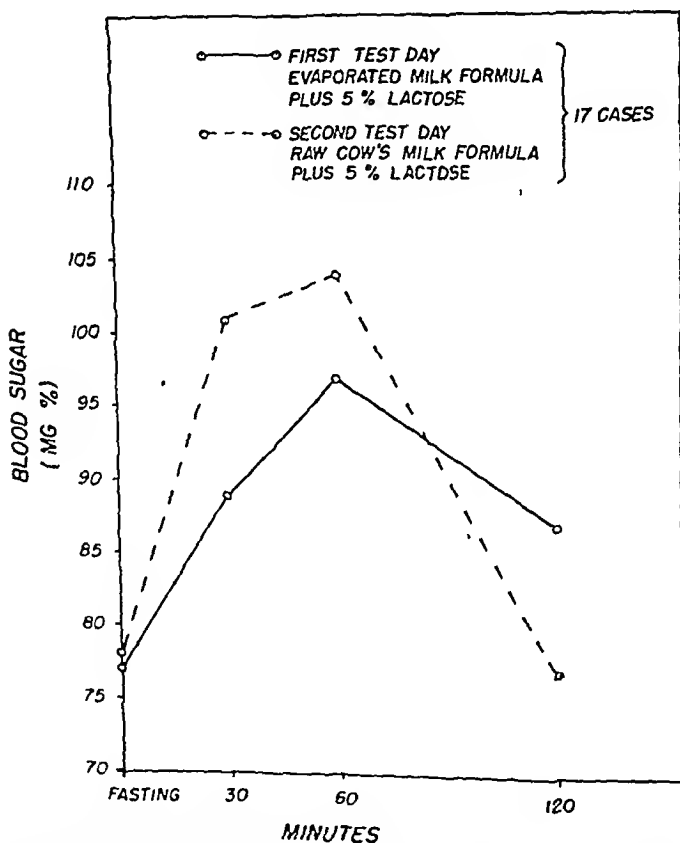


Fig. 7.—Comparison of average blood sugar tolerance curves for normal infants on lactose administered in evaporated milk formula and raw cow's milk formula.

In this study we avoided the use of heated mother's milk, for in our experiments we found that rapid changes take place in mother's milk even on standing at reduced temperatures, as measured by rapid loss of phosphatase activity. We chose the more stable certified raw cow's milk as representing unchanged cow's milk.\* We carefully checked the phosphatase activity of this milk by the Scharer method<sup>6</sup> to ensure that it had not been pasteurized

\*The raw cow's milk used was Walker Gordon Certified Raw Cow's Milk.



previously, and compared it against the standard hospital formula. The raw milk contained approximately 1,000 Scharer units per milliliter whereas the hospital formula contained no phosphatase activity, as would be expected.

In a series of seventeen infants we compared the blood sugar tolerance curves obtained with evaporated milk formula (1 part evaporated milk to 2 parts of water) with 5 per cent lactose supplement, and with raw cow's milk formula (2 parts raw milk to 1 part of water) with 5 per cent lactose supplement. From Fig. 7 it is apparent that the sugar tolerance curve of the raw cow's milk formula resembles more closely the sugar tolerance curve obtained with raw mother's milk than does the curve obtained with the evaporated milk formula.

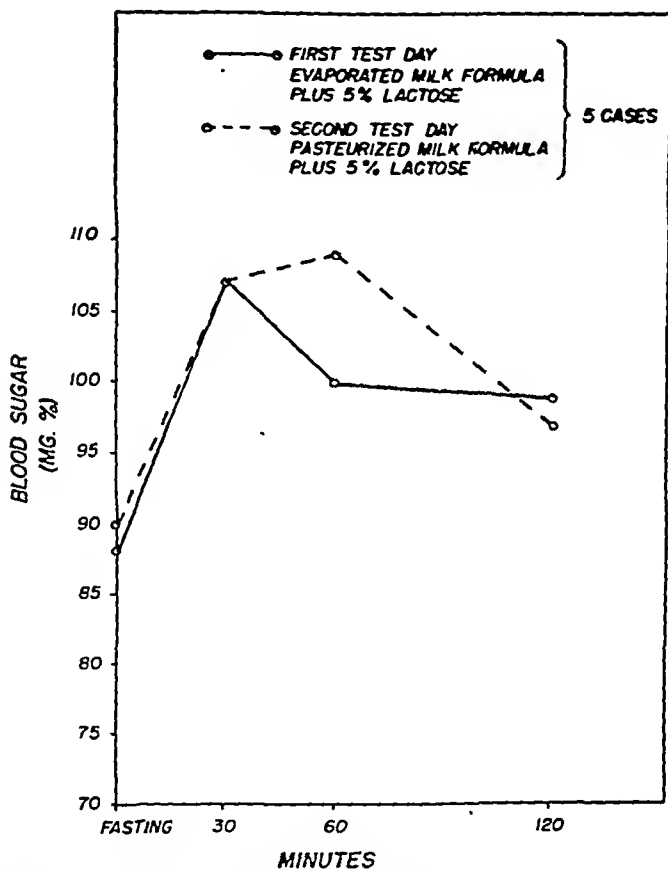


Fig. 8.—Comparison of average blood sugar tolerance curves for normal infants on lactose administered in evaporated milk formula and pasteurized milk formula.

Thus, our observation that lactose produced sugar tolerance curves with low peaks was again confirmed when lactose was fed in an evaporated milk mixture. However, when lactose was administered in raw milk, the blood sugar tolerance curve assumed the general shape of that produced by the monosaccharides and that produced by lactose in raw mother's milk. Lactose

with raw cow's milk was given on the second test day to the same infant to avoid possible changes in the intestinal flora due to the administration of a raw milk. The results are valid, for lactose, whether given on the first or second test day, showed similar tolerance curves (see Fig. 6). Also our controls (see Fig. 4) showed little variation from first to second test day on the same infant.

The question was raised as to whether it was valid to compare the effects of evaporated milk and raw cow's milk since they were physically dissimilar due to the treatment of the evaporated milk. Therefore, we extended the study to the comparison of the sugar tolerance curves produced by lactose in evaporated milk formula (one part evaporated milk, two parts water, 5 per cent lactose supplement) to that produced by lactose in whole pasteurized milk formula (2 parts whole pasteurized milk, 1 part water, 5 per cent lactose supplement). Fig. 8 indicates that little difference exists in this respect between pasteurized and evaporated milk.

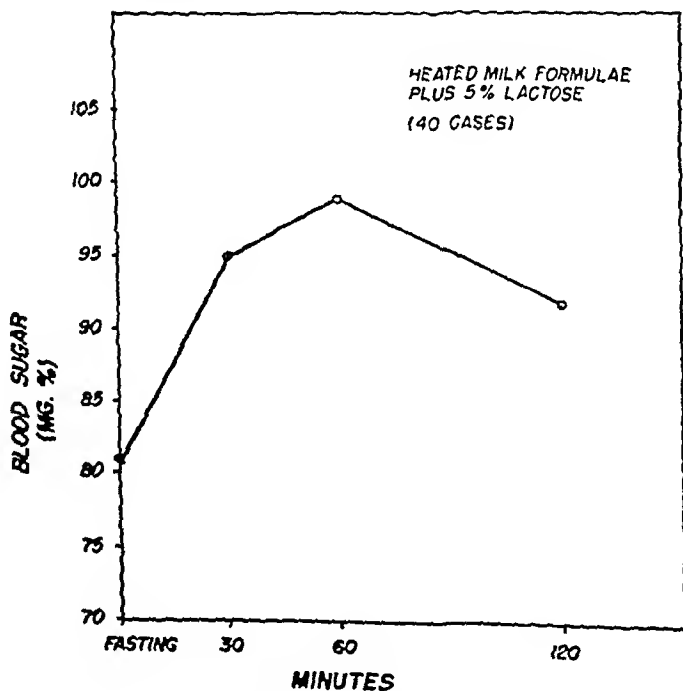


Fig. 9.—Average blood sugar tolerance curve for forty normal infants on lactose administered in heated cow's milk formulae.

In the curves above, thirty-four individual tolerances are reported using lactose added to treated milk formulas. In addition, we have performed six additional tolerances using lactose in evaporated milk, not reported herein. Thus we have carried out forty blood sugar tolerances using lactose in treated milks. This number appears large enough to warrant the conclusion that lactose will produce tolerance curves with low peaks and slow return to the fasting level as shown in Fig. 9.

## DISCUSSION

From Figs. 1, 2, and 3 it is evident that the characteristic growth curve in the neonatal period does not differ appreciably among the three groups of infants observed. The greatest loss of weight occurred during the first twenty-four hours. This was followed by a lesser weight loss, no weight loss, or a slight gain during the next twenty-four hours. Thereafter there was a steady gain throughout the period of observation. Thus, the statistical minimum weight occurred on the third day of life (taking the day of birth as the first day of life).

Table I indicates that the average birth weight of male infants was greater than that of female infants. This is in agreement with observations previously reported.<sup>7</sup> Further, the net change in the weight of male infants at the end of seven days, expressed as a percentage of the birth weight, was algebraically greater than that of female infants. No statistically significant difference in net change from birth weight was observed among the three groups. The breast-fed infants with feedings supplemented with evaporated milk formulas did not have a sufficiently large representation for comparison with the other two formulas. The "post cibum" feeding used was the basic hospital formula (1 part evaporated milk and 2 parts sterile water) supplemented with either 5 per cent Cartose or 5 per cent Dextri-Maltose. The weight statistics of all breast-fed infants were pooled to obtain the figures in Table I. This was done in making up the table because the results obtained comparing the two carbohydrate supplements in evaporated milk formulas indicated no significant differences between the two.

The breast-fed group was drawn mainly from the general obstetrical service nursery of the hospital. This was necessary because of the fact that a very small percentage of the mothers on private service breast feed their children. Thus this group of breast-fed infants represents essentially a group in a less privileged financial status.

We noted that the average growth curve of the first thirty male infants on basic hospital formula with Cartose supplement showed a marked net gain at the end of seven days. But when these figures were averaged together with the entire series, there was shown a much lower net gain for the seven-day period. When approximately one-half the total number of cases had been tabulated (532 cases), examination of the net change in weight at the end of seven days indicated that the breast milk feeding supplemented with starch hydrolysates was superior to Cartose in evaporated milk formula, which in turn was superior to Dextri-Maltose formula (Table II). On final tabulation (Table I) the reverse order was observed.

These observations indicate the inherent danger of drawing conclusions from averages of a short series in this type of study. The number of cases for a proper study of this type should run into many thousands, and we decided that it would be uneconomical from our point of view.

It may be noted that in this study no difference was observed in the conditions of the stools, buttocks, or general well-being of any of the infants on the three different formulas.

TABLE II. NET DIFFERENCE BETWEEN BIRTH WEIGHT AND WEIGHT AT SEVEN DAYS IN RELATION TO THE TYPE OF FEEDING AT MIDPOINT OF STUDY (532 CASES)

FORMULA	SEX	NO. CASES	AVERAGE BIRTH WEIGHT	PER CENT CHANGE AT 7 DAYS
Evaporated milk with 5 per cent	M	170	7.362	-0.42
Cartose	F	152	7.177	-0.98
Evaporated milk with 5 per cent	M	37	7.456	-0.62
Dextri-Maltose	F	51	7.101	-1.21
Breast milk supplemented with	M	61	7.357	+0.27
Cartose or Dextri-Maltose formula	F	61	7.205	-0.78

A study comparing different milk formulas by means of sugar tolerance curves on the same infant on succeeding days seems to be a more useful tool than the method of statistical growth curves. Fig. 4 indicates that even in a group as small as six infants reproducibility may be obtained from one day to the next using the same formula. This method, therefore, allows one to use the same infant, employed to test the formula, as a control.

The natural lactose found in mother's milk produced a blood sugar tolerance curve with a peak rise of approximately 50 mg. per cent higher than the fasting level as shown in Fig. 5. Further, the blood sugar level returned almost to the fasting level at the end of a two-hour period. Assuming that milk from a healthy mother is the ideal feeding for the infant, this curve can be taken as a criterion which should be duplicated when feeding an artificial milk formula.

In Fig. 6 it is seen that the lactose curve showed a peak rise of 18 mg. per cent over the fasting level. Moreover, the return to fasting level was delayed, the final level at the end of two hours still remaining at a much higher percentage of the peak level than the final level shown by the mother's milk (see Fig. 5). On this same chart (Fig. 6), the starch hydrolysate produced a curve approximating the shape of that produced by mother's milk, with a rise of 27 mg. per cent above the fasting level, but a closer return to the fasting level at the end of two hours.

The curve produced by raw mother's milk or by starch hydrolysate in evaporated milk could be approximated, however, when lactose was administered in raw cow's milk as shown in Fig. 7. Because of the importance of this finding, we extended this study to seventeen cases (thirty-four tolerance studies in all). Here, again, lactose produced lower peaks and a slower return to fasting level when administered in evaporated milk formula.

Fig. 8 illustrates a short study done on five cases (ten sugar tolerances) to see whether evaporated milk had some peculiarity in which it differed from pasteurized milk. It is evident even in this short series that there is no significant difference between the two milks in so far as the tolerance curves with lactose are concerned. The peak rise for evaporated milk was almost identical with that produced by pasteurized whole milk, being approximately 19 mg. per cent in both cases. In both cases, the blood sugar level returned to approximately 50 per cent of the peak rise at the end of two hours. This is distinct from lactose in raw mother's milk, where the drop was 80 per cent

of the peak rise, and lactose in raw cow's milk, where the drop was approximately 100 per cent of the peak rise at the end of two hours (see Figs. 5 and 7).

The blood sugar tolerance curve produced by starch hydrolysate in evaporated milk formula resembles that produced by lactose in raw cow's milk (see Figs. 6 and 7).

That lactose will produce its own characteristic tolerance curve when administered in heated cow's milk formulas is firmly established by the summary of the forty cases shown in Fig. 9. This is in agreement with the findings with lactose administered in water (ten cases) reported by Schlutz and collaborators.<sup>5</sup>

It is evident from our results that there is some ingredient or factor in raw cow's milk that will enable lactose to produce a sugar tolerance curve resembling that produced by raw mother's milk. This is not present in evaporated milk or in milk which has been pasteurized to the extent that the phosphatase activity has been destroyed. There are at least two hypotheses possible. One is that an enzyme is present in raw milk which aids in the splitting and/or the absorption of lactose by the intestinal tract. The other hypothesis is that the heating in the process of pasteurization may produce a change of the physical state of the mixture which interferes with absorption.

The ideal formula for a newborn mammal would most likely approximate the natural milk of that species. It is well known that the carbohydrate in human milk is lactose. The nutritional value and the side-effects of lactose have been studied in infants.<sup>8-11</sup> Several investigators<sup>12-14</sup> have studied the effect of alpha-lactose and beta-lactose upon the state of the intestinal flora and fecal conditions, indicating that lactose seems to be necessary for the normal growth of *Lactobacillus bifidus* in the intestine. Schimansky stated that the conversion of beta-lactose to the alpha-isomer is a function of the intestinal wall.<sup>14</sup> Malyoth<sup>13</sup> has found that intestinal *L. bifidus* cultures are formed in a shorter time and in greater purity after feeding infants beta-lactose than after mother's milk. The relation of lactose to fat metabolism has been emphasized by several investigators.<sup>15, 16</sup> Lactose supplies not only glucose but galactose. The function of the latter in normal human metabolism has not been clarified. Galactose is known to occur in cerebrosides and kersasin.

Thus it appears that there should be several advantages to the use of lactose in the diet of the infant. Our observations would imply that the medium in which the lactose is administered should have an important bearing on the relative value of this carbohydrate supplement. In the rat, both beta-lactose and the alpha-isomer are absorbed from the intestine at the same rate, and both produce undesirable effects such as alopecia, growth failure, and diarrhea.<sup>17, 18</sup> It would be of interest to see what the effects would be if the lactose were administered in raw milk.

The findings that raw milk produced different sugar tolerance curves than the heated milks may be in some way related to the observations of several investigators that there is better growth on raw mother's milk than on heated

mother's milk.<sup>19-21</sup> A few experimental observations are reported in the literature which show no difference between the two or a slight advantage for heated mother's milk.<sup>22, 23</sup> This latter group, when closely examined, is shown to consist of experiments with small numbers of infants over relatively short periods of time. For example, Kayser showed only seven cases with a slight advantage for heated milk.<sup>22</sup> His measure was weight gain. In view of the above observations that such studies are invalid unless large numbers of cases are used, the results of his study are in question. Kujath<sup>23</sup> studied twenty-nine infants, of whom ten subsequently died, six received heated, and 4 received raw milk. The remaining nineteen was too small a number upon which to draw conclusions, although a slight favor for unheated mother's milk was shown. Ladd and collaborators<sup>24</sup> claim advantages for raw cow's milk over pasteurized milk. Our growth studies should not be compared with the studies referred to above. Our statistical studies extended over a seven-day period only, while the studies referred to concern themselves with growth for longer periods of time.

In our study we took the phosphatase activity of raw milk as the criterion of its unchanged condition. We found that untreated mother's milk taken at a collecting station early in the morning and delivered to us at noon had already lost a great deal of its phosphatase activity. Upon analysis, the mother's milk was found to contain from 36 to 43 Scharer units per milliliter, whereas the phosphatase values in raw cow's milk run about 1,000 Scharer units per milliliter. It was also observed that there was a physical change in mother's milk on handling. Milk obtained from the collecting center after having been packaged and delivered by messenger, when allowed to stand in the refrigerator overnight, appeared as though the fat had been churned into butter. If milk is administered in this form, with the colloidal state disturbed, there is a probable reduced absorbability of fats.<sup>25</sup>

Recently, while the present study was in progress, a publication appeared<sup>26</sup> in which the conclusion was reached that artificial cow's milk formulas produced better growth in premature infants than mother's milk. Close examination of this publication shows that it involved 122 infants, of whom sixteen were on mother's milk. Weight changes were used as an index of the value of the formula. Examination of the substance which was called "mother's milk" showed that it was quite remote from the mother's milk that issues from the breast. These investigators boiled the milk for five minutes. The milk would then fall into the category of a pasteurized milk in which the ingredients necessary for proper utilization of lactose may be destroyed. Second, no B-complex vitamins were added to the milk to make up for the vitamins destroyed in the boiling treatment. Third, the milk was strained after boiling, which removed at least some of the proteins and fat, thus removing it from the category of whole milk. From our observations in handling mother's milk, we feel that this sort of treatment tends to coagulate the fats into larger globules. It has been observed that the nature of the dispersion and the particle size are important considerations in the absorption of the fat-soluble vitamins.<sup>27, 28</sup> The breaking of the natural milk emulsion

probably results in an interference with the absorption of fats and fat-soluble vitamins.

Any study comparing mother's milk with an artificial formula can be made only by feeding the infant at the breast and weighing him before and after feeding, unless proper precautions are taken to preserve the original character of the milk. Several studies of this type have appeared in the literature, particularly the series of studies by Catel.<sup>21, 29, 30</sup> He found in a large series of premature infants that untreated mother's milk was superior to pasteurized mother's milk, and that there was better growth and lessened mortality. He also found that freezing raw mother's milk was a satisfactory method of preservation as opposed to pasteurization.<sup>31</sup> Freezing the milk does not destroy the enzymes or the vitamins, nor does it affect its digestibility for the premature infant. It must be pointed out that pasteurization does not destroy all the enzymes of raw milk. For example, it does not destroy the catalase or reductase.<sup>32</sup>

#### CONCLUSIONS

1. Growth studies on 1,227 infants for the first seven days of life, fed on evaporated milk formulas supplemented with starch hydrolysates, and breast-fed infants who received a supplement formula, were carried out.

2. No significant differences were demonstrated between the two different starch hydrolysates (Cartose and Dextri-Maltose) and breast feeding, using the statistical growth curve as a criterion.

3. The same infant on two successive days shows a fairly close correlation in blood sugar tolerance curves using the same formula feeding on both days, and this procedure may be used as a test for comparing various carbohydrates.

4. Raw mother's milk (containing 7 per cent lactose) produces a sugar tolerance curve characterized by a relatively high peak and a return to almost the fasting level at the end of two hours.

5. Sugar tolerance curves obtained when lactose is administered in evaporated or pasteurized milk formulas show relatively low peaks and a delayed return to the fasting level.

6. Lactose, when administered in raw cow's milk formula, exhibits a sugar tolerance curve which resembles more closely that produced by using raw mother's milk than that produced by using lactose in heated cow's milk formulas.

7. Starch hydrolysates, when administered in evaporated milk formula, produce sugar tolerance curves which resemble those produced by lactose in raw cow's milk formula.

8. These results would imply that a factor is present in raw milk which is destroyed on heating and which will influence the shape of the tolerance curve obtained with lactose when administered to newborn infants.

9. The disappearance of this factor must not be interpreted as signifying that raw milk is superior in nutritional value to artificial milk formulas. Further investigation is needed in this direction. Our statistical studies have revealed no difference in nutritional value between breast milk and artificial formulas.

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## FUNGUS STUDIES IN ATOPIC DERMATITIS

### FAILURE TO DEMONSTRATE PATHOGENIC FUNGI IN THE LESIONS

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IN examination of infants and children suffering from atopic dermatitis, physicians are bound to encounter lesions which in clinical appearance suggest a superficial fungus infection, that is to say, lesions which are not numerous, are roughly and sharply circumscribed with scaling and an apparent tendency to clearing in the center. Indeed, in the absence of any positive history of atopy in the patient's family and failing the signs of a true atopic dermatitis in such regions of the body as the antecubital and popliteal spaces, one sometimes must consider mycotic infection in differential diagnosis. Therefore, it has seemed worth while to employ modern methods once again to ascertain whether pathogenic fungi or immunologic evidence of fungus infection could be found in a series of cases of atopic dermatitis.

It is generally accepted that fungous infection is not an etiologic factor in producing the lesions of atopic dermatitis. However, a few studies have been conducted to test the moot point whether fungi play any active part in the causation of so-called infantile eczema. Among such studies might be mentioned those of Hill,<sup>1</sup> Bruno Bloch,<sup>2</sup> Benham and Hopkins,<sup>3</sup> White,<sup>4</sup> and Pennington.<sup>5</sup>

#### PROCEDURE

A series of sixty-eight infants and children (thirty-three female and thirty-five male) with atopic dermatitis, who had not yet received any treatment, were studied. No attempt was made to separate those whose lesions resembled the superficial mycoses and others whose lesions did not. Scrapings of the lesions were taken from various parts of the body. These were (a) mounted in a 10 per cent sodium hydroxide solution and were examined microscopically; and (b) were cultured on Sabouraud's medium.

Intradermal tests were carried out with extracts of five of the more common fungi encountered in New York; namely, *oidiomyces* (1 to 100), *trichophyton* (1 to 30), *Aspergillus glaucus*, *Rhizopus*, and *Penicillium notatum*. The amount employed was 0.02 c.c. of extract (enough to produce the smallest wheal) intradermally and a first reading taken after fifteen minutes for evidence of an immediate reaction; a second reading was taken forty-eight hours later for a delayed, tuberculin-type reaction.

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## RESULTS OF THE STUDY

Not one of the sixty-eight patients studied showed a positive reaction of either immediate wheal or delayed tuberculin-type to the extracts employed. (1) Microscopic examination of the scrapings taken from the lesions on various parts of the skin and treated with a 10 per cent sodium hydroxide solution failed to disclose any evidence of hyphae. (2) Cultures upon Sabouraud's medium, of scrapings of the lesions, failed to reveal the presence of any pathogenic fungi. The nonpathogenic fungi and bacteria found were penicillium species (one), *Aspergillus niger* (one), pink torula (two) bacteria (mostly saprophytic staphylococci) (eleven), other unidentified saprophytes (one), no growths fifty-two, with a total of sixty-eight.

## CONCLUSION

The reported study confirms the generally held opinion that pathogenic fungi do not play a role in determining the clinical appearance of some lesions in atopic dermatitis. In the entire series of sixty-eight cases, not a single instance of a pathogenic dermatophyte was recovered. All skin tests for immediate wheal reaction and for forty-eight-hour tuberculin-type reaction with the extracts of fungi enumerated above were negative.

The author wishes to express his appreciation for the helpful suggestions and criticism rendered by Morris Leider, M.D., in charge of The Allergy Department at The New York Skin and Cancer Unit.

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# FLUORESC EIN CIRCULATION TIME IN NORMAL AND PATHOLOGIC CONDITIONS IN INFANTS AND CHILDREN, INCLUDING VARIOUS TYPES OF CONGENITAL MALFORMATIONS OF THE HEART

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THE circulation time is the measured interval between the injection of a test substance into the circulatory system and its recognition by various methods. Substances with varying physical and physiologic end points have been used in the past to determine the circulation time. Many of these substances depend upon the subjective response of the patient. In infants and children it is often necessary and desirable to use a substance with which one can accurately determine the time without depending upon any subjective response. The fluorescein circulation time appears to satisfy this requirement. The simplicity of the procedure and the nontoxic properties of the test substance (sodium fluorescein) are further advantages.

The fluorescein circulation time was described by Lange and Boyd<sup>1</sup> in 1942 to determine the adequacy of the circulation in bowel obstructions and peripheral vascular diseases. They also stressed its diagnostic value in congestive heart failure, hypo- and hyperthyroidism, and suggested its clinical application in the diagnosis of congenital cardiovascular anomalies.

Sodium fluorescein is a resorcinolphthalein compound which is nontoxic when injected intravenously, and emits a brilliant green fluorescence when viewed under the long wave ultraviolet lamp. It is rapidly excreted unchanged through the kidneys, giving a varying degree of brilliant green discoloration to the urine, depending upon its pH.<sup>2</sup> Relatively large amounts may be given in a single intravenous dose,<sup>1</sup> although in a few instances in our subjects it was noted that nausea and occasional vomiting may accompany doses of more than 4 c.c. regardless of weight of the patient.

## PROCEDURE

The procedure was used on age groups varying from 15 days to 13 years. The calculated dose was approximately 0.7 c.c. per ten pounds of body weight of a solution containing dilution 5 per cent sodium fluorescein in 5 per cent sodium bicarbonate\* as compared to Lange and Boyd's 0.7 c.c. per 10 kg. of body weight. The antecubital vein was selected as the site for injection and was entered with a 21-gauge needle. The room was darkened and the ultraviolet lamp was concentrated on the lips. The dye was injected as rapidly as possible, injection time averaging less than one second. The time interval between the beginning of the injection and the first appearance of a brilliant green fluorescence of the mucous membranes of the mouth was measured with a stop watch. The first appearance

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\*Manufactured commercially as "Fluorescite" by C. F. Kirk Co., New York, N. Y.

of this fluorescence was used as the end point, but a rapidly spreading fluorescence of the entire body resulted in all cases.

This report includes a series of 107 patients, fifty-seven of whom had demonstrable cardiac pathology and fifty who had no demonstrable cardiac disease. Of the former group, thirty-two conditions were congenital in origin and twenty-five were acquired.

## RESULTS IN FIFTY NONCARDIAC CASES

In Table I it is shown that the arm-to-lip time varies with age. The circulation time from neonatal period through 2 years varied from 5 seconds to 8.5

TABLE I. CIRCULATION TIME IN NONCARDIAC CASES

PATIENT	AGE	W/FIGHT (L.B.)	DIAGNOSIS	AMOUNT (C.C.)	TIME (SEC.)
D. S.	4 mo.	11	Resolving pneumonia	1	7
J. M.	7 mo.	13	Resolving pneumonia	1	5
R. McC.	7 mo.	17	Resolving pneumonia	1	6
R. E.	9 mo.	17	Resolving pneumonia	1	6
C. H.	9 mo.	18	Resolving pneumonia	1.5	8.5
S. C.	12 mo.	20	Pulmonary tuberculosis	1.5	6.5
J. H.	12 mo.	23	Subglottic obstruction	1.5	5
J. J.	14 mo.	25	Normal	2	7.5
K. L.	19 mo.	28	Pneumonia	2.5	7
P. G.	20 mo.	29	Pneumonia	2	5
A. H.	22 mo.	33	Normal	2.5	7
S. McE.	2 yr.	27	Pulmonary tuberculosis	1.5	5
F. L.	2 yr.	21	Cerebrospastic	1.5	6
C. J.	2 yr.	27	Tuberculosis with effusion	2	9
K. D.	3 yr.	41	Melena	3	5
C. R.	3 yr.	22	Tuberculosis with effusion	1.5	6
D. J.	3 yr.	29	Pneumonia	2	7
N. H.	3 yr.	35	Cerebellar ataxia	2.5	8
D. J.	4 yr.	36	Epilepsy	2.5	6.5
A. K.	4 yr.	40	Pulmonary pneumonia	3	5.5
S. H.	5 yr.	40	Asthma	3	6
G. L.	5 yr.	41	Normal	3	7
G. J.	5 yr.	31	Laryngotracheitis	2.5	9
C. E.	5 yr.	39	Pulmonary tuberculosis	2.5	7.5
F. K.	5 yr.	40	Chronic bronchiectasis	3	9
W. L.	6 yr.	39	Normal	3	7.5
W. Y.	6 yr.	41	Pulmonary tuberculosis	2.5	9
G. K.	7 yr.	49	Chronic nephritis	3	6
R. C.	7 yr.	55	Tonsillitis	4	6.5
M. P.	7 yr.	50	Otitis media	4	7
R. S.	7 yr.	38	Tuberculosis	2.5	8.5
J. W.	7 yr.	50	Dermatitis medicamentosa	3.5	9.5
M. N.	8 yr.	58	Dermatomyositis	4	7.5
M. W.	8 yr.	50	Pneumonia	3.5	6.5
A. W.	8 yr.	57	Acute glomerular nephritis	4	7.5
B. L.	8 yr.	56	Histoplasmosis	4	8
F. C.	8 yr.	73	Erythema multiforme	5	10
G. F.	9 yr.	105	Nephritis	5	7
J. D.	9 yr.	51	Nonspecific adenitis	3.5	8.5
J. B.	10 yr.	80	Suspicious tuberculosis hilus	5	11
E. N.	10 yr.	96	Resolving pneumonia	5.5	12.5
C. C.	10 yr.	70	Epilepsy	5	13
A. P.	11 yr.	71	Diabetes	5	9
T. P.	11 yr.	60	Epilepsy	4	11
C. R.	11 yr.	59	Pulmonary tuberculosis	4	13
D. S.	12 yr.	86	Cervical adenitis	5	7
K. P.	12 yr.	70	Erythema multiforme	5	10.5
J. D.	12 yr.	79	Normal	4.5	10.5
D. J.	12 yr.	66	Tuberculosis with effusion	4.5	12
J. M.	13 yr.	75	Diabetes	5	7.5

seconds, with an average of 6.5 seconds. From 3 years through 13 years it varied from 5.0 seconds to 12.5 seconds, with an average of 8.5 seconds. The work of Witzburger and Cohen<sup>3</sup> on normal infants and children showed an average of 7 seconds in those from one to 24 months and an average of 11.5 seconds in the children from 3 to 13 years. In the older age group our series presented a more rapid circulation time than was found by Witzberger and Cohen. This variation may possibly be due to the larger amounts of sodium fluorescein used in our study.

Chronic or even acute pulmonary pathology, such as childhood tuberculosis, pneumonia, or asthmatic bronchitis produced no appreciable variation in the circulation time.

#### RESULTS IN FIFTY-SEVEN CARDIAC CASES

The circulation time of the cardiac cases as shown in Table II varies according to age just as in the noncardiacs. However, in congenital anomalies with a venous-arterial shunt there is a marked shortening of the circulation time, irrespective of age. In tetralogy of Fallot and transposition of the great vessels

TABLE II. CIRCULATION TIME IN CONGENITAL CARDIAC CASES

PATIENT	AGE	WEIGHT (LB.)	DIAGNOSIS	AMOUNT C.C.	TIME (SEC.)
P. W.	15 days	8	Interauricular septal defect	1	4.5
R. K.	3 mo.	12	Tetralogy of Fallot	1	2.5
S. C.	3 mo.	8	Tricuspid atresia, pulmonary stenosis, interauricular septal defect	1	3
M. M.	3 mo.	12	Interventricular septal defect	1	4
R. V.	5 mo.	12	Tetralogy of Fallot	1	4
B. O.	9 mo.	19	Tetralogy of Fallot	1	4
J. N.	9 mo.	18	Tetralogy of Fallot	1	5
S. A.	9 mo.	12	Possible pulmonary atresia	1	5
K. G.	14 mo.	20	Complete transposition of great vessels	1	2.5
B. F.	18 mo.	25	Common auriculoventricular valve	2	3
R. O'N.	18 mo.	17	Interauricular with mitral stenosis	1.5	7
R. O'N.	20 mo.	21	Interauricular septal defect	1.5	8.5
C. F.	21 mo.	37	Double aortic arch	2	5
M. J.	21 mo.	36	Interauricular defect	2.5	14
R. O'N.	22 mo.	21	Interauricular septal defect	1.5	9
R. McG.	2 yr.	25	Tetralogy of Fallot	1.5	3.5
R. H.	3 yr.	35	Tetralogy of Fallot	2.5	4
L. A.	4 yr.	40	Patent ductus	3	6.5
F. H.	5 yr.	41	Coarctation of aorta	3	7
P. M.	6 yr.	43	Patent ductus or interauricular septal defect	3	7
C. B.	6 yr.	50	Coarctation of aorta	3.5	6
M. W.	7 yr.	55	Complete transposition of great vessels	3.5	2.5
S. M.	7 yr.	55	Coarctation of aorta	4	7
D. C.	8 yr.	60	Tetralogy of Fallot	4	5
W. J.	9 yr.	53	Coarctation of aorta	4	9.5
L. G.	10 yr.	58	Coarctation of aorta	4	12
R. T.	11 yr.	95	Patent ductus or interauricular defect	6	9.5
J. S.	12 yr.	77	Lutembacher's syndrome	5	10
J. S.	12 yr.	77	Lutembacher's syndrome	5	11
G. F.	13 yr.	75	Tetralogy of Fallot	5	5
P. H.	13 yr.	110	Coarctation of aorta	5	9.5
P. H.	13 yr.	110	Coarctation of aorta	5	10.5

the time is shortened 3.0 to 4.4 seconds, with an average of 3.7 seconds. In other congenital anomalies, such as patent ductus Botalli, interauricular and interventricular septal defects, the circulation time was not altered in any appreciable amounts for the respective age groups.

The reason for the shortening in this former group, i.e., tetralogy of Fallot, etc., is that the blood as it enters the right side of the heart is shunted immediately into the systemic circulation via the dextraposed or transposed aortic vessel, thereby completely by-passing the pulmonary circuit. There is no change in the circulation time in isolated septal defects, due to the fact that the pressure is normally greater on the left side of the heart, thereby preventing any right-to-left blood flow. The amount of dye injected is small in comparison to the total blood volume and does not alter the already existing left-to-right shunt. The dye must, therefore, go through the pulmonary circuit before entering the systemic circulation; the reduction of the circulation time is definitely a diagnostic aid in determining the presence of a dextraposed or transposed aortic vessel.

TABLE III. CIRCULATION TIME IN ACQUIRED CARDIAC CASES

PATIENT	AGE (YR.)	WEIGHT (LB.)	DIAGNOSIS	AMOUNT C.C.	TIME (SEC.)
D. M.	2	28	Myocarditis	2	7
C. A.	4	40	Rheumatic heart disease	2.5	5
D. N.	4	40	Rheumatic heart disease	2.8	7
C. T.	4	38	Rheumatic heart disease	2	7
R. S.	5	45	Rheumatic heart disease	3.5	6.5
A. R.	5	50	Rheumatic heart disease with decompensation	3.5	12
A. G.	5	40	Rheumatic heart disease	2.5	8
V. B.	6	35	Rheumatic heart disease	2.5	9
C. N.	6	50	Rheumatic heart disease with decompensation	3.5	20
T. H.	7	48	Rheumatic heart disease	3	7.5
R. S.	7	48	Rheumatic fever	3	9
B. C.	8	58	Rheumatic fever	4	7
L. B.	8	55	Rheumatic heart disease	4	8
B. S.	9	51	Rheumatic heart disease	3	7
I. B.	9	50	Rheumatic heart disease	3.5	8.5
K. W.	9	65	Rheumatic heart disease	4.5	13.5
R. S.	10	65	Rheumatic heart disease	5	8.5
I. D.	10	60	Rheumatic heart disease	4	10
S. H.	10	60	Rheumatic heart disease	4	11
B. P.	10	60	Rheumatic heart disease with decompensation	4	21
H. B.	11	75	Rheumatic heart disease	5	11
W. F.	11	50	Rheumatic heart disease	4	13
O. W.	11	50	Rheumatic heart disease	4	13
J. D.	12	75	Rheumatic fever	5	10
E. J.	12	60	Rheumatic heart disease	4	11.5

There is no appreciable alteration of the normal circulation time in acute or convalescent rheumatic heart disease, as was shown in Table III. The average time for the acquired cardiac group was 9.2 seconds as compared to 8.5 seconds in the noncardiac group. However, in the presence of congestive heart failure there is marked prolongation of the circulation time.

## SUMMARY AND CONCLUSIONS

1. The fluorescein circulation time, i.e., the time between the injection of fluorescein into the arm vein and the first appearance of the dye on the patient's lips, was measured in 107 patients.

2. In the normal noncardiac group, the average circulation time from the neonatal period through 2 years of age was 6.5 seconds. From three years to 13 years, the average was 8.5 seconds.

3. In tetralogy of Fallot where the aorta is dextraposed, or in complete transposition of the great vessels where the aorta comes off the right ventricle, as well as in tricuspid atresia with an interauricular defect, the fluorescein circulation time is markedly shortened to an average of 3.7 seconds.

4. The fluorescein circulation time is not appreciably altered in interauricular or interventricular septal defects or in patent ductus Botalli, coarctation of the aorta, or Lutembacher's syndrome.

5. The circulation time is not appreciably altered in acute or convalescent rheumatic heart disease except in congestive heart failure, where it is definitely prolonged, with an average of 17.7 seconds as compared to an average of 9.2 seconds in the compensated cases.

6. The fluorescein circulation time in infancy and childhood is a simple, nontoxic, inexpensive, objective procedure.

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# AMELIA: REVIEW OF LITERATURE AND REPORT OF CASE

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CONGENITAL absence of all four extremities, known as amelia or amelus, is one of the more rare congenital anomalies. Few cases have been reported and little is known regarding the etiology of this tragic malformation. In view of the recent renewed interest in all congenital anomalies and their relationship to the virus diseases, we feel it timely to review the literature of this anomaly, add a case which has been under our observation, and discuss briefly the present concept as to causation.

In a review of the literature for a period of 100 years, we have been able to find authentic reports of only thirteen infants born with absence of all extremities. These cases<sup>1-12</sup> are tabulated in Table I. It can be seen that re-

TABLE I. AMELIA: REVIEW OF LITERATURE

AUTHOR	YEAR	NO. CASES
Vrolik <sup>1</sup>	1855	1
Hare <sup>2</sup>	1858	1
Slingenberg <sup>3</sup>	1908	1
Grassi <sup>4</sup>	1909	1
Price <sup>5</sup>	1928	1
Lukjanow <sup>6</sup>	1930	1
Lereboullet et al. <sup>7</sup>	1932	1
Levy <sup>8</sup>	1941	1
Killingsworth and Engledow <sup>9</sup>	1942	1
Otero <sup>10</sup>	1944	1
Hedenstedt <sup>11</sup>	1944	2
Mooney <sup>12</sup>	1946	1

ports have been sporadic. The most recent case reported is that of Mooney<sup>12</sup> who discusses a family with multiple absences of extremities, and includes without comment a picture of one child born without either arms or legs. To this rather scattered series, we wish to add the following case.

## REPORT OF CASE

A. J., a white female infant was admitted to Lincoln Hospital at the age of 12 days from the hospital in which she was born, because of absence of the arms and legs. She was the second child of American parents; the father was 28 years old, the mother 23 years old. The mother's first pregnancy resulted in a normal spontaneous delivery of a full-term female child in December, 1945. This child appeared normal at birth, and her development, both mental and physical, has been average. The last menses prior to the second pregnancy began on April 29, 1947. There was no illness during any part of this pregnancy; the mother was vaccinated against smallpox, with primary take, on April 14, 1947. Diet during pregnancy appears to have been normal. She delivered a full-term infant on Feb. 7, 1948, after an uncomplicated labor of two hours' duration; birth weight of the child was 2,420 Gm.

From the Pediatric Service of Dr. Harry S. Altman at the Lincoln Hospital.



The infant was transferred to this hospital for care on Feb. 19, 1948. Examination at that time revealed the general condition of the patient to be good; weight was 2,330 Gm. Search for congenital anomalies revealed none except for amelia (Fig. 1). Head circumference was 35.5 cm.; chest 32 cm.; abdomen 28 cm.; and total length 35.5 cm. Heart and lungs were normal.



Fig. 1—Patient A. J., aged approximately 2 months. Note presence of small stump of right arm and toe-like appendage representing left lower extremity.

Anus was patent. Nose, throat, and ears were normal. The left arm was completely absent, only a bud about 5 mm. in diameter being visible. The right arm was represented by a stump about 3 to 4 cm. long, which appeared to contain bone, and which could be moved by the patient. Shoulder girdles were present, and their mobility seemed normal. The right lower extremity was indicated only by a small, soft-tissue mass 1.5 cm. in diameter. The left lower

extremity was absent except for one toelike appendage with slight indentation of the distal end and two rudimentary nail beds. Hip girdles were present and appeared to have normal surrounding musculature; some attempt to move the rudimentary toe was made. X-ray examinations (Fig. 2) confirmed the presence of bone in the right upper and left lower extremity regions; the upper end of the right humerus was present, as were small bones representing one toe. Shoulder and pelvic girdles appeared roentgenographically normal for her age.



FIG. 2.—Patient A. J., reproduction of x-rays of upper (top) and lower (bottom) portions of body, showing absence of extremities except for stump of right humerus, and toelike appendage on left.

The course in the hospital was punctuated by frequent episodes of elevated temperature, for which no adequate explanation could be found, either clinically or by laboratory methods. However, her general condition was always good, and, on June 23, 1948, at the age of 4½ months, she was released

at the request of the parents, who desired to care for her at home. At this time her weight was 2,950 Gm.; she was quite active within her limitations, moving her head and the shoulder and pelvic girdles; her mental development appeared normal for her age.

The patient was readmitted on July 21, 1948 (aged 5 months), because of high fever of twelve hours' duration. On admission, her temperature was 108° F. per rectum; as before, she did not appear acutely ill and there were no positive findings to explain the elevation. Her weight was 3,100 Gm. With symptomatic therapy only, her temperature was reduced, became normal after two days, and then assumed an irregular course varying from 99° F. to 102° F. for the next two weeks. Complete laboratory work-up revealed no cause. At this point (aged 5½ months), she was again taken home by her parents. Her weight on discharge was 3,700 Gm.

Ten days after this second admission, the patient suffered another sudden rise in temperature to 106° F., and was taken to another hospital where she expired after twenty-four hours. No post-mortem examination was allowed, and it was the impression at the other institution that termination was caused by bronchopneumonia.

#### DISCUSSION

Arey<sup>13</sup> states that the buds which will form the extremities appear first during the fifth week of gestation (7 to 8 mm. fetus). These buds increase in size, the distal end of each flattens, and successive constrictions occur, so that the three parts of the extremity become apparent; grooves then indicate the position of the digits. These changes occur between the sixth and eighth weeks (approximately 11 to 25 mm. fetus). Differential growth subsequently results in the normal extremity. Meanwhile (Patten<sup>14</sup>), the primordium of the skeleton of the extremities appears as condensations of mesenchyme during the early part of the sixth week (12 mm. fetus); later during this week, some molding occurs, so that the positions of the main bones are suggested. The process of cartilage and bone formation then occurs.

Little actually is known in regard to causation of departures from this normal process of development of the extremities. It is hardly necessary to review here the numerous older theories, most of which are now discarded. Considerable attention has been given to the idea of developmental arrests, and this concept can explain the mechanism, if not the cause, of many anomalies.

The concept of developmental arrest depends upon the understanding that the rates of development of different parts of the embryo, and of the embryo as a whole, vary. Rapid progress alternates with relative inactivity. Within each developing part there is a critical short period of rapid multiplication, during which time this part differentiates and during which it dominates all other activity in the embryo. If anything interferes completely or in part with this process, the dominance is lost and is never regained; the next region then assumes its role and in turn becomes dominant. The result is an imperfect or even absent region, depending upon the time and degree of interference.

This concept of development is an interesting one in the light of which to consider the present case. We must postulate that during, probably, the sixth week of gestation, something interfered with the critical moment of differentiation of the extremities. This particular time-period is suggested by the evidence that limb budding apparently did start, and that some condensation of mesenchyme did occur, leading to an abortive laying down of

bone (right upper extremity and left lower extremity). It is reasonable to assume that the process need not be equally advanced in all extremities, and this would account for the varied stages of arrest.

Carrying the hypothesis one step further, it is possible that intercurrent disease in the pregnant woman, with its effect upon the embryo, could afford an opportunity for such developmental arrest, and the virus diseases recently incriminated in the production of anomalies fit into this category. We, therefore, inquired carefully into the history of the pregnancy which produced the child reported. We could find no evidence of rubella or of any other virus disease during early pregnancy. The fact that the mother was vaccinated was mentioned in the case report for the sake of completeness; the time relationship of the vaccination to the pregnancy rules it out as a factor.

With regard to the hyperthermia noted repeatedly in this infant, no definite explanation or mechanism can be offered. It is believed that a heat regulating center is present in the midbrain, which may prevent extreme rises in body temperature. Mechanically, control is a product of heat production versus heat loss by the body (Smith<sup>15</sup>). It was felt that poor control might have been a result of rednead skin surface for radiation of heat. However, there was also a lack of one of the major mechanisms for production of heat, to wit, contraction of the extremity muscles. Further elements in the heat regulation may be the sympathetic nervous system and the effect of adrenalin upon muscular activity. Which factor or factors may have been at fault here can merely be conjectured.

#### SUMMARY

Thirteen known cases of amelia, congenital absence of all extremities, are reviewed from the literature. An additional case is reported, with clinical and roentgenographic findings; an interesting feature of this case was the manifestation of unexplained, intermittent hyperthermia. A brief summary of the present-day concept of production of congenital anomalies in general, and amelia more specifically, is presented.

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## SOLITARY RENAL ECTOPIA AND THE NEPHROTIC SYNDROME

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ALTHOUGH renal ectopia is a congenital anomaly, one is struck by the infrequency with which this condition is mentioned in pediatric literature. The majority of reports are confined to urologic and surgical journals and texts and only Campbell contributes a comprehensive discussion on this subject for the pediatrician in his classic volumes of *Pediatric Urology*. The paucity of discussion on this subject in pediatric literature is particularly surprising in view of the fact that a great deal of what has been learned about congenital urinary tract anomalies has been acquired through the study of autopsy material on infants and children. Furthermore, symptoms and physical findings resulting in urologic studies occurred in infants and children in many of the case reports of ectopic kidney recorded in the literature. Also, congenital renal ectopia may offer a diagnostic problem such as occurred in our case before urologic studies were completed. Of further interest in our case is the nephrotic syndrome, and it was because of edema and albuminuria that the infant was hospitalized. To our knowledge, the nephrotic syndrome and solitary ectopic kidney have not appeared in the literature prior to this report.

### CASE HISTORY

A 21-month-old male infant was admitted to Sarah Morris Hospital on March 30, 1948, for observation relative to generalized edema and albuminuria.

Five days before admission the mother noticed some puffiness of the eyelids, frequency of urination, and excessive thirst.

*Previous History.*—When he was 7 months of age his mother noticed frequent episodes of body shaking but no loss of consciousness; these episodes subsided spontaneously over a period of several months. At 9 months of age an eczematoid eruption of the extremities was observed. It was apparently due to egg sensitivity, and cleared after withdrawal of this food. The patient's 5½-year-old sister suffers from hay fever. At 11 months of age the patient was hospitalized for a severe streptococcus throat infection. At the onset his temperature was 105° F. and he had three convulsions in a period of six hours. He was treated with sulfadiazine and penicillin and made an uneventful recovery. One month later he developed a severe case of chicken pox with a maximum temperature of 104 to 105° F. for two days, but no convulsions occurred. At 14 months of age he experienced two severe attacks of bronchial asthma. At this time he was found to have an idiosyncrasy to barbiturates. He was not seen again until the onset of the present illness at 21 months of age.

*Physical Examination.*—Physical examination revealed a somewhat thin white male infant who did not appear ill. His weight was 26½ pounds and height 32½ inches. His temperature was 100° F. There was a moderate puffiness of the upper eyelids, the abdomen was large, dullness was present in both flanks, and a fluid wave was elicited. Pitting edema of the feet, ankles, and

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legs was present. A mild eczematoïd eruption was present over both legs. The ears appeared normal. There was a clear mucoid discharge in both nostrils and the nasal mucosa appeared slightly boggy. The tonsils and pharynx appeared normal. The lungs were clear and the heart was normal. In spite of considerable abdominal distention and ascites, a mass was palpated in the abdomen. It was about the size of a medium-sized orange, apparently lobulated, firm, freely movable, and located low in the left lower quadrant about two inches to the left of the midline. No other masses were felt in the abdomen. Rectal examination revealed no impacted feces, and the mass could be palpated bimanually in the region of the sacrum between the finger inserted in the rectum and the hand on the anterior abdominal wall. Both testes were in the scrotum and no masses were palpated in the inguinal canals.

The initial impression was that of an intra-abdominal neoplasm, possibly renal in origin, omental cyst, a mass of mesenteric lymph nodes, probably malignant, or a hydronephrotic or cystic kidney. Further studies revealed the true nature of the pathology.

*Laboratory Examination.*—Urinalysis (Table I) revealed a grade 4 albuminuria, cylinduria, and an occasional red blood cell and white blood cell. Examination of the blood revealed no evidence of anemia. There was a slight increase in serum urea nitrogen, a marked hypoproteinemia, primarily due to reduction in albumin, and hypercholesterolemia (Table II). The blood pressure was 110/70. These findings are typical of the nephrotic syndrome and probably in this case are associated with a mild glomerulonephritis. In addition, however, a catheterized specimen of urine obtained during cystoscopic examination revealed on culture, *Escherichia coli* and *Aerobacter aerogenes*, indicating in all probability a secondary ascending infection resulting from obstruction of the urinary tract.

TABLE I. URINE

DATE	WEIGHT (LB.)	PH	SPECIFIC GRAVITY	ALBUMIN*	CASTS†	RBC†	WBC†
3/30/48	27	6.0	1.010	4	0	0	1-2
4/1	25½	7.0	1.008	4	0	3-4	2-3
4/2				4	occasional hyaline	3-4	3-4
4/5	25½	7.0	1.012	3	occasional hyaline	3-4	3-4
4/6	300 c.c. PLASMA			3			
4/12	27	6.5		4	0	3-4	many
	250 c.c. PLASMA						
4/13	26½	7.0	1.018	2	2	1-3	8-10
4/16	26¾	6.5	1.018	2	0	1-2	3-4
	250 c.c. PLASMA						
10/18	31	6.5	1.007	2	0	3-5	1-3
10/20		6.0	1.013	3	1-2 granular, occasional hyaline	1-2	4-5
10/28	250 c.c.		WHOLE BLOOD				
11/1		6.5	1.011	2	occasional granular	1-3	5-8
11/5		6.0	1.014	2	occasional hyaline	4-6	1-2
2/1/49	32	6.0	1.012	2	occasional hyaline	1-3	5-6

\*Grade 1 to 4 denoting severity.

†Microscopic examination of centrifuged urine, high power field.

TABLE II. BLOOD CHEMISTRY

DATE	UREA NITROGEN (MG./ 100 ML.)	CHOLESTEROL (MG./ 100 ML.)	PER CENT EST.	TOTAL PROTEIN (GM./ 100 ML.)	ALBUMIN (GM./ 100 ML.)	GLOBULIN (GM./ 100 ML.)
3/30/48	28.0	260	66.0	4.0	2.7	1.3
4/5	23.5	416	65.0	5.4	3.4	2.0
4/12	32.0	503	62.0	4.7	2.3	2.4
4/16	38.0	584	52.0	5.3	2.7	2.6
10/18	37.0	358	67.5	5.9	2.5	3.4
10/30	34.5	---	---	---	---	---
11/5	43.5	---	---	6.3	2.5	3.8
2/1/49	29.0	306	70.0	6.9	3.4	3.5

An intravenous pyelogram revealed, at the end of five minutes, a moderate amount of opaque media overlying the left sacroiliac region and suggestive of an ectopic kidney (Fig. 1, A). There was no evidence of dye excretion on the right side. The amount of dye continued to accumulate until a large amount was present at the end of forty-five minutes (Fig. 1, B and C), at which time a large amount of dye was present in the urinary bladder. The bladder appeared normal except for the fact that external pressure was demonstrated on the upper and left borders, apparently due to the ectopic left kidney (Fig. 1, C).

Cystoscopic examination (I.J.S.) revealed that the bladder urine was grossly clear and the capacity and tolerance of the bladder was good.

The mucosa appeared normal throughout. The left ureteral orifice was normally placed and normal in appearance. It was easily catheterized with a No. 4 ureteral catheter for a distance of 15 cm. At the site of the normal right ureteral orifice there was a small dimple that could not be entered with either a catheter or a bougie. The urine from the left kidney was grossly clear and indigo-carmin injected intravenously appeared through the catheter in the left ureter only.

After retrograde instillation of 15 c.c. of Hippuran solution through the ureteral catheter, roentgenograms demonstrated the pelvis and calyces of a single ectopic kidney overlying the left sacroiliac region. There was dilatation of the pelvis and calyces and of the upper portion of the ureter, indicating hydronephrosis. Narrowing of the ureter was seen just inferior to the ureteropelvic junction, and this may represent a defect due to congenital stricture, or a congenital band or vessel (Fig. 2). However, the ectopic kidney was mobile so that it was felt possible that the ureteral defect was due to kinking.

On the basis of the excretion urogram, cystoscopic examination, and retrograde pyelogram, a diagnosis of left ectopic kidney was established. The kidney, which lay over the left border of the sacrum at the pelvic brim, was enlarged and mobile. Palpation suggested that it was lobulated. Although there was some degree of hydronephrosis, function was fairly good, as evidenced by good excretion of dye and only slight retention of blood urea nitrogen.

Since no kidney or ureter was visualized on the right side, and on cystoscopic examination no right ureteral orifice could be demonstrated, it was our belief that there was no right kidney or ureter. However, without exploration congenital solitary kidney is difficult to differentiate from agenesis or nonfunctioning kidney due to aplasia or atrophy.

The patient was treated with a high protein, low sodium diet, transfusions of irradiated plasma,\* and infusions of Amigen. After eighteen days he was discharged from the hospital clinically improved.

During the following six months he was readmitted to the hospital several times for treatment because of increased edema and albuminuria, which on two

\*Plasma is irradiated in order to destroy hepatotoxic virus that may be present. (Samuel Deutsch Convalescent Serum Center.)



Fig. 1—4. Intravenous pyelogram reveals at the end of five minutes, a moderate amount of opaque media overlying the left sacroiliac region, suggestive of an ectopic kidney.  
*B.* Accumulation of dye at the end of twenty minutes.  
*C.* Accumulation of dye at the end of forty-five minutes, at which time a large amount of dye is present in the urinary bladder and the bladder appears normal except that evidence of external pressure is demonstrated on the upper and left borders, apparently due to the enlarged ectopic left kidney.



occasions followed in the course of upper respiratory infections. The degree of albuminuria varied from 2 to 4 plus and the urinary sediment showed little change from the original findings.

On Oct. 18, 1948, approximately 6½ months after his initial admission, he was readmitted to the hospital for exploratory laparotomy. During the previous six weeks he was without visible edema and appeared in good health. However, the mass had increased somewhat in size, and appeared partially outlined against the left lower abdominal wall (Fig. 3). The increase in serum urea nitrogen, and consistently present red blood cells, white blood cells, and casts in the urinary sediment indicated that, in all probability, there had been further damage to the kidney (Tables I and II). A repeated intravenous pyelogram revealed little change over the findings noted on April 7, 1948, except possibly for a slight increase in the degree of hydronephrosis.



Fig. 2.—Retrograde pyelogram demonstrates the single left ectopic kidneys in the sacroiliac region. The calices, pelvis, and upper part of the ureter are visible. There is hydronephrosis. Narrowing of the ureter is present just inferior to the pelvis, and this may represent a defect due to a congenital stricture, or a congenital band or vessel.

On Oct. 26, 1948, a transperitoneal exploration of the left kidney was done (I.J.S.) A large kidney protruding anteriorly toward the abdominal wall was found in the left pelvic region. The retroperitoneum covering the kidney was incised longitudinally and dissected free both laterally and medially. The kidney was retracted laterally and the pelvis was observed to be enlarged. The ureter was markedly dilated and tortuous, and at the ureteropelvic junction there was a pronounced angulation and narrowing. Palpation of this area gave the impression that the muscularis was absent and was replaced by fibrous tissue. At

the lower pole of the kidney a large vessel was palpated, apparently arising from the left external iliac artery. There was no encroachment upon the ureter in the region of this stricture. Adequate mobilization of the kidney was not possible and correction of the angulation of the ureter could not be accomplished. Exploration of the right side through the same incision confirmed the preoperative diagnosis of absent right kidney. The child made an uneventful recovery and was discharged from the hospital on Nov. 5, 1948, ten days postoperatively. At this time there was no edema. The urine contained 2 plus albumin, an occasional finely granular and hyaline cast, and occasional red and white blood cells. The urea nitrogen was 43.5 mg. per cent, the total serum protein 6.3 mg. per cent, the albumin fraction 2.5, and globulin 3.8 mg. per cent. He was re-examined on Feb. 1, 1949, three months postoperatively. There was no edema. The urine contained 2 plus albumin, and the findings on microscopic examination were unchanged. The urea nitrogen had fallen to 29 mg. per cent. The total serum protein was 6.9 mg. per cent, the albumin 3.4, and the globulin 3.5 mg. per cent.



Fig. 3.—The patient at 2 years, 3 months of age, five months after the initial hospitalization, and one month before exploratory operation. Edema and ascites have subsided. There is a visible prominence in the left lower abdomen, which is palpable as the ectopic kidney.

#### DISCUSSION

Congenital renal ectopia is not common but probably occurs more frequently than one is led to believe, because unless complications such as infection, stone or pain associated with urinary symptoms, or the finding of an abdominal mass occur, this anomaly may go unrecognized.

Campbell, in 1930, found twenty-seven instances of congenital renal ectopia in 14,400 autopsies in adults at Bellevue Hospital. Adding these to others reported in the literature, he found seventy-two cases in 47,477 collected autopsies, an incidence of one in approximately 600 individuals. In 12,080 autopsies in children, there were fifteen cases, an incidence of one in 800.<sup>1</sup> If one can visualize the number of cases which go unrecognized during life and realize the great number which never come to autopsy, one can easily conceive that the incidence must be considerably higher.

Solitary renal ectopia is apparently extremely rare. Stevens,<sup>2</sup> after a comprehensive review of the literature in 1937, estimated that solitary kidneys occurred once in every 700 to 1,610 cases, pelvic ectopia once in 2,150 to 3,000 cases, and solitary pelvic kidney once in 22,000 autopsies. He collected twenty-five reports of solitary pelvic kidney from the literature and added two cases of his own. Since this publication, eight more cases were found by Zuker,<sup>3</sup> who added a case of his own, making the total number of cases reported through 1946, thirty-six.

Other urologic anomalies frequently coexist with renal ectopia, particularly with the solitary variety. The anomalies may involve the upper or lower urinary tract or the genitalia, and it is not uncommon to find anomalies in other organs of the body.<sup>4</sup> Therefore, a careful examination of the entire body is indicated whenever renal ectopia is found.

Due to compensatory hypertrophy, the structural volume of the solitary kidney often approximates that of two normal organs and its functional output is increased correspondingly.<sup>4</sup> Hypertrophy and hydronephrotic dilatation were responsible for the large size of the kidney in our case.

Although congenital absence of one kidney is not incompatible with health, a single kidney is more likely to be the seat of disease than two normal kidneys. Pyelonephritis, hydronephrosis, and death by renal failure occur in rather a high percentage of these cases.<sup>4</sup> Fortune<sup>5</sup> reports 22.6 per cent kidney disease in 422 collected autopsy cases of solitary kidney as against the general autopsy average of 15 per cent. In Anders'<sup>6</sup> series of 170 cases of solitary kidney, seventy-nine kidneys were diseased.

The complication of the nephrotic syndrome is of extreme interest and added further difficulties in the management of our case. Although it has already been established that infection occurs more often in a solitary kidney than in twin kidneys, there is no evidence that points to congenital anomalies of the upper urinary tract as predisposing to glomerulonephritis or nephrosis. The nephrotic syndrome in our patient can best be explained as occurring in association with glomerulonephritis and secondary to the previous upper respiratory infections. The allergic phenomena and drug idiosyncrasies suffered by this patient may also be contributing factors in the etiology of the nephrotic syndrome.

In addition to the nephrotic syndrome and glomerulonephritis, our patient unquestionably has hydronephrosis and probably some degree of pyelonephritis secondary to the ureteropelvic obstruction. Because it was impossible to correct the underlying congenital ureteropelvic deformity, there is no reason to believe

that chemotherapy or antibiotic therapy will permanently eliminate the pathogenic organisms cultured from the urine. Consequently, the ultimate prognosis is poor, and in all probability, the hydronephrosis and pyelonephritis will progress.

### CONCLUSIONS

Congenital ectopic kidney occurs at autopsy in approximately one to 600 or 800 individuals. Considering the number of cases of congenital ectopic kidney that are unrecognized, the actual incidence is probably a great deal higher than the autopsy incidence. Solitary ectopic kidney is extremely rare, but in view of the fact that disease is more prone to occur in such a kidney during early life, its recognition is more likely to occur during infancy or childhood.

The presence of an abdominal mass in an infant or child, particularly in the lower quadrants, should suggest the possibility of an ectopic kidney. Erroneous diagnosis of neoplasm, mesenteric cyst, mesenteric adenitis, appendicitis, ileocecal tumor, tuberculosis, etc., can be avoided by thorough urologic study in all cases of abdominal mass with or without urinary symptoms, and/or a pathologic urine. A simple clinical test that may aid in the establishment of diagnosis of a kidney mass is that of palpation or massage, which frequently will produce transient albuminuria in a patient whose urine was previously clear.<sup>4</sup>

Although operative intervention proved to be a failure in our case, and apparently will be in most instances of solitary ectopic kidney, there is always the possibility that a coexisting anomaly may be corrected. Therefore, when anomalies of the ureter and hydronephrosis exist, we believe that exploration is justified. If correction is not possible, destruction of the kidney and renal failure ultimately will occur.

### SUMMARY

A case of solitary pelvic ectopic kidney observed in a 21-month-old infant is reported. The infant was seen initially because of the nephrotic syndrome, and the ectopic kidney was found on subsequent examinations. On the basis of laboratory findings, it was believed that the nephrotic syndrome was associated with glomerulonephritis. Surgical exploration confirmed the clinical findings. Hydronephrosis secondary to congenital angulation of the ureter and ureteropelvic obstruction was present. Due to anomalous blood supply, mobilization of the kidney and correction of the ureteral deformity could not be accomplished.

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## Case Reports

### ANOMALOUS ORIGINS OF THE RIGHT COMMON CAROTID AND RIGHT AND LEFT SUBCLAVIAN ARTERIES ASSOCIATED WITH EISENMENGER'S COMPLEX

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THIS case of anomalous origins of the subclavian arteries and the right common carotid artery in association with Eisenmenger's complex has various interesting characteristics both from the anatomical and embryologic points of view.

#### CASE REPORT

This 5-month-old female infant was well until two days before her hospital entry, when she developed a respiratory infection which seemed to be localized mostly in the chest. At the onset of her illness there were fever and cough. The day before hospital entry she began to vomit and continued to do so all that day and the following day. There was no history of cyanosis.

The past history revealed that the child had been treated in The Children's Hospital Dispensary for an infection of the upper respiratory passages two months before. There had been impetigo and thrush at 3 months of age. The child had been considered to be a Mongolian idiot since birth.

Prenatal history revealed that the mother had vomited throughout the entire pregnancy. The delivery and neonatal period were normal.

The maternal grandparents were deaf mutes and there also was a history of diabetes in the maternal antecedents.

Physical examination at the time of hospital entry revealed a well-nourished and well-developed white female child with Mongoloid facies. There was a wide neck which was continuous with the occiput. The pharynx was injected. The chest was symmetrical. Rough breath sounds and rhonchi were heard and the respirations were labored. The heart rate was normal, the heart was not enlarged to percussion, and no murmurs were heard. The fifth digits of the hands were rather short and curved toward the ring fingers.

A chest film taken on the day of entry showed an increased radio-opacity over the upper three-fourths of the left chest. There was also a dense hilar shadow on the right which was thought to represent an enlarged lymph node.

The child did poorly during her hospital stay. The temperature spiked to 105° F. on the second and fourth hospital days. In spite of penicillin and sulfadiazine therapy the child died.

*Necropsy Findings.*—The body was that of a well-developed and well-nourished white female infant of stated age measuring 60 cm. in length and weighing 4.88 kg. The eyes were slightly slanted and there were bilateral epicanthal folds. Even in death the muscles were extremely hypotonic. There was very little rigor mortis even at four hours. The thumbs inserted at right angles to the hands; however, there were no simian lines. There was no Mongolian spot at the base of the spine.

Upon entering the thoracic cavity, the heart was seen to be extremely large. The great veins entered in normal fashion. The aorta appeared to emerge

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more to the right than normal. There was no innominate artery; instead the right common carotid and subclavian arteries arose from the aorta, side-by-side, at the same level. The left common carotid artery arose from the aorta immediately above the latter. The ductus arteriosus arose from the pulmonary artery, proceeded cephalad anterior and to the left of the left main bronchus and entered the aorta at the arch. The left subclavian artery arose from the middle of the ductus arteriosus. The latter structure was 7 mm. in length. That portion of the ductus on the pulmonary artery side was anatomically closed while the lumen on the aorta side was as large as the subclavian artery which arose from it.

Upon opening the heart it was noted that the musculature of the right ventricular wall was one-half again as thick as that of the left ventricle. The valve measurements were as follows: tricuspid 6.5 cm., pulmonary 3.7 cm., mitral 5.0 cm., aortic 3.0 cm. There was a large interventricular septal defect measuring 2.7 by 1.2 cm. which occurred in the pars membranacea of the septum. The aorta was dextroposed and the right wall was immediately above the septal defect. The valves contained their normal numbers of leaflets and the coronary arteries arose normally.

The posterior aspects of both lungs were red-purple in color and quite hard to the touch. The middle portions of both lungs were dark red in color and firm. The anterior portions of both lungs were light pink in color and crepitant. On section the posterior portions showed marked infiltration with blood, the middle portions were very dark pink in color, and fluid could be expressed from the cut surfaces. The anterior sections appeared normal.

The liver was enlarged, light in color, and appeared edematous.

The brain was somewhat smaller than the cranial vault and showed evidence of cerebral agenesis.

The remainder of the organs were within normal limits.

*Microscopic Examination.*—In the lungs, the walls of the alveoli were thickened and the capillaries were engorged. Some serous fluid and a few cellular elements were present in the lumina of a number of the alveoli. Mononuclear cells and a rare polymorphonuclear leucocyte were present in the interstitial tissue.

The muscle fibers of the heart muscle were separated, showing very distinctly the branching of the myocardial fibers. There were some rather large nuclei present.

Histologically the remainder of the organs showed a generalized red cell engorgement.

*Discussion.*—Origin of the left subclavian artery from the ductus arteriosus is described by Taussig<sup>1</sup> in association with absence of the aortic arch. The origin of the latter anomaly is ascribed to the overmigration of the heart in its caudad movement. In the case described, the left subclavian artery arose from the center of the ductus arteriosus; however, the aortic arch was present.

Since both the right subclavian and the right common carotid arteries arose side-by-side from the aorta and rotated through 90 degrees from their usual relations and also since the left subclavian artery arose from the ductus arteriosus, it might be inferred that, in its embryological development the heart migrated farther caudad than normal enough to rotate the arteries on the right through the 90 degrees and sufficiently to cause the left subclavian artery to arise from the ductus arteriosus, but not sufficiently to cause the descending aorta to become continuous with the pulmonary artery, with consequent obliteration of the aortic arch.

The external appearance of the heart and the anomalous origins of the arteries are shown by the drawing in Fig. 1. The over-all blood circulation is

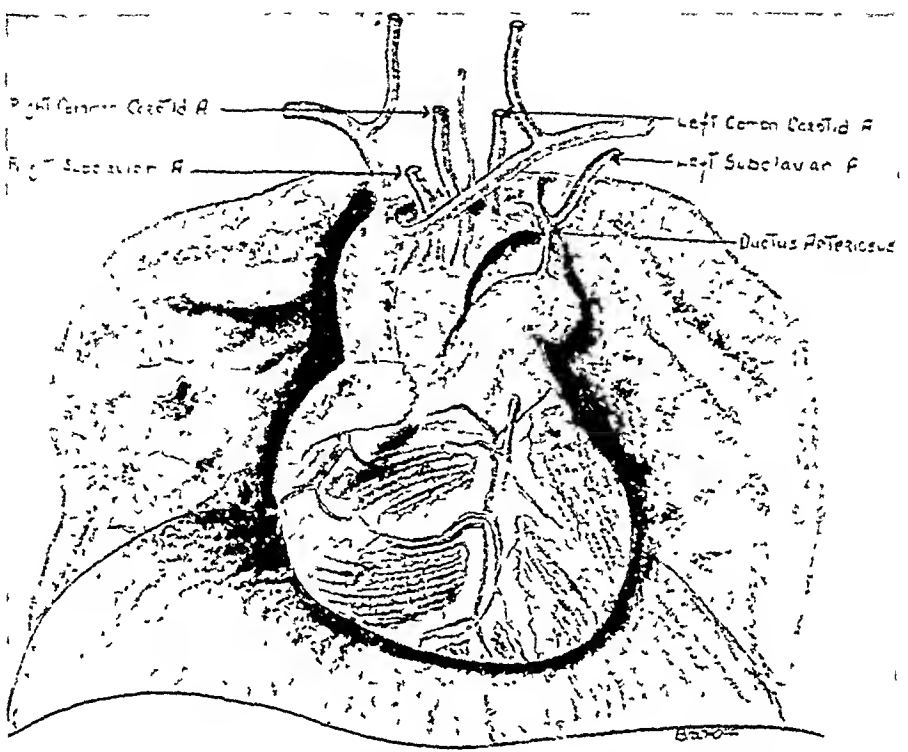


Fig 1—Drawing showing external appearance of heart and anomalous vessels

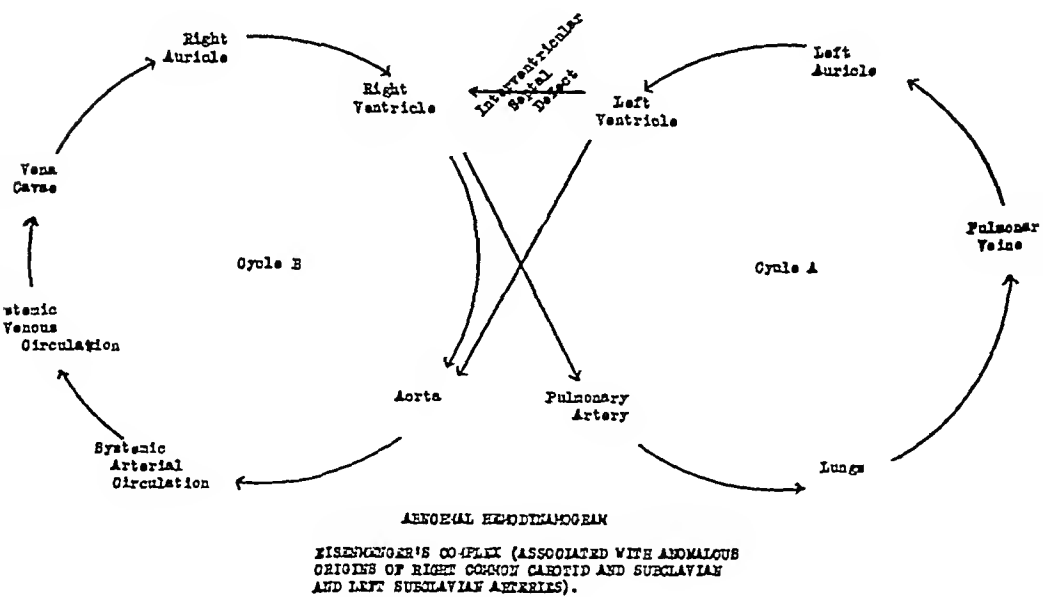


Fig. 2.

shown by the hemodynamogram<sup>2</sup> in Fig. 2. The dextroposition of the aorta is shown by the paired arrows going to the aorta from the right and left ventricles and naturally means that blood from both ventricles reaches the aorta.

Considering the heart under discussion, where the aorta did not actually override the septal defect, there would be less tendency for unoxygenated blood from the right ventricle to escape into the aorta. One might consider, however, that a Venturi effect existed which would draw unoxygenated blood into the aorta as the fast-moving stream of blood passed the orifice in the ventricular septum.

Blood will pass from an area of higher pressure to an area where the pressure is lower, hence the arrow depicting the interventricular shunt is drawn as passing from Cycle A to Cycle B, i.e., from the left ventricle to the right. This would follow the normal picture where the pressure within the left ventricle is higher than the pressure within the right ventricle. However, a fact which should not be neglected in the case under discussion is that pressure exerted upon a fluid is transmitted equally in all directions. Considering the fact that the right ventricular wall was one-half again as thick as the left, having potentially greater muscular power available, the pressure within the right ventricle should have been higher than that in the left ventricle, and unoxygenated blood should have passed from Cycle B to Cycle A.

Since cyanosis did not dominate the clinical picture, we might infer that the amount of unoxygenated blood reaching the systemic circulation by way of the interventricular septal defect and by direct injection into the aorta must have been at a minimum. Undoubtedly, as data are accumulated on intracardiac pressure studies the directions of blood flow will be elucidated.

#### SUMMARY

1. A case of anomalous origins of the right common carotid and right and left subclavian arteries associated with Eisenmenger's complex in a Mongolian idiot, is presented.
2. Some embryological considerations are reviewed in an attempt to explain the probable source of the anomalous origins of these vessels.
3. Theoretical considerations of the direction of blood flow are discussed in an attempt to correlate the clinical picture with the anatomical findings.

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## DEEP VEIN THROMBOSIS IN A NEWBORN INFANT

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DEEP venous thrombosis in the extremities during infancy and childhood is an extremely rare occurrence. Search of both American and foreign literature on the subject fails to reveal a single instance of peripheral venous thrombosis in this age group unaccompanied by serious systemic infection or marasmus consequent on a debilitating disease. In a thorough review of pulmonary embolism and infarction in infancy and childhood, Zuschlag<sup>1</sup> studied thirty-eight cases from the Mayo Clinic, only four of which were associated with thrombus formation in the major channels of the extremities. All of these involved the femoral vein and were associated with severe infection either in close proximity to the affected veins or at some distant location. Zuschlag<sup>2</sup> further gathered sixty-four cases of pulmonary infarction in the younger age groups from the literature. Among these, only two were associated with thromboses in peripheral veins, one each in the femoral and crural veins. The former occurred in a 4½-year-old child in the course of severe measles,<sup>3</sup> and the latter in a 9-year-old child who also had pericarditis, myocarditis, and thrombosis of the longitudinal sinus.<sup>4</sup>

The following case is reported because of its uniqueness in the absence of any demonstrable local or systemic infection, and because an unusual diagnostic procedure in this age period was employed successfully as corroborative evidence of the clinical diagnosis.

### CASE REPORT

L. P., a 9-day-old white male infant of Jewish parentage, was admitted to the Mount Sinai Hospital Pediatric Service on June 3, 1947, because of cyanosis and swelling of the right lower extremity of twenty-four hours' duration. The infant was the product of an uncomplicated full-term pregnancy and delivery, and throughout his first eight days he appeared normal in all respects. A ritual circumcision was performed on the eighth day of life at the maternity hospital. During the procedure the patient's grandfather, who was described as an unusually large and powerful man, held the infant about the upper thighs with thumbs pressed in the region of the inguinal folds. At one point during the operation the grandfather was reprimanded because of the unusual pressure which his thumbs appeared to be exerting in both inguinal regions of the baby. Another less enthusiastic member of the group held the infant during the remainder of the ceremony. There was no unusual bleeding, nor were any other difficulties encountered in the actual operative procedure.

Nine hours after the circumcision and twenty-four hours prior to admission the mother noted the infant's extremities to be cool and slightly bluish. This did not alarm her at the time, but during the succeeding twelve hours the right lower extremity became progressively colder, more deeply cyanotic, and definite swelling was noted. During this period the left leg regained its normal color and again became warm. There appeared to be no impairment of the baby's general condition, he took his breast feedings well, moved all his extremities actively, appeared in no distress, and remained afebrile.

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Physical examination on admission revealed a well-developed and nourished lusty male infant who did not appear ill. The rectal temperature was 99° F., pulse 120 per minute, and respirations 30 per minute. The patient was very active and moved all his extremities through their full range. With the exception of the penis, right lower extremity, and skin over the lower abdomen, the examination was negative. The glans penis was mildly ulcerated with minimal fresh bleeding from its surface. There was no evidence of infection, and the penile shaft was of normal color and warmth. The right lower extremity was cyanotic and cool from Poupart's ligament anteriorly, and posteriorly from the major gluteal fold. The entire leg was edematous but no pitting could be demonstrated. The circumference of the midthigh was 3 cm. greater than a similar point on the opposite extremity, and the right calf circumference exceeded that of the left by 2 cm. No femoral pulsation could be felt on the right, but with pressure over any point on the leg immediate blanching occurred with rather slow restoration of the previous cyanotic color as the pressure was released. The skin over the right lower abdomen was definitely dusky, and in this area there were several prominent veins in which the blood flow was cephalad. There were, in addition, multiple fine telangiectases in the same region.

*Laboratory.*—Hemoglobin was 14.5 Gm. per 100 c.c.; white blood cells were 20,000 with 65 per cent mature polymorphonuclear leucocytes, 3 per cent non-segmented leucocytes, 25 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophiles. Platelets numbered 200,000 per cubic millimeter, and there were less than 0.5 per cent reticulocytes. The bleeding time was 2½ minutes, clotting time 4½ minutes with good clot retraction at the end of one hour. The urine was normal. A roentgenogram of the abdomen and lower extremities revealed only soft tissue swelling of the right lower extremity.

*Course.*—The patient's general condition remained excellent throughout his seventeen-day hospital stay, there was no fever at any time, feedings were taken well, and weight gain was satisfactory.

The findings on admission suggested venous obstruction involving the major vessels of the right lower extremity, possibly extending into the right iliac vein, in addition to arterial spasm in this member and possibly some element of lymphatic stasis. The evidence appeared to favor phlebothrombosis rather than thrombophlebitis and an operative procedure with ligation of the affected vessel was considered. However, in view of the uncertainty regarding the nature and extent of the pathology, a period of observation was decided upon, and at the same time heparinization of the infant was started. Intravenous heparin in a dosage of 1 mg. was administered at hourly intervals for twenty-four hours, with prolongation of capillary clotting time from an initial four minutes to eighteen minutes. At this point, twenty-four hours after hospitalization, the right lower extremity was definitely warmer than on admission, was less edematous and cyanotic, and a good femoral pulse could be made out on this side. No abnormalities had appeared in the left lower extremity. The telangiectasia over the right lower abdomen had increased, dilated venules now were seen around the umbilicus and also above Poupart's ligament just to the left of the midline. From this point intramuscular heparin was to be administered at eight-hour intervals, but through an oversight which was not detected for twenty-four hours it was omitted. Nevertheless, the capillary clotting time during the period of omission of heparin continued prolonged, varying between twelve and fifteen minutes. Forty-eight hours after admission to the hospital improvement in the leg had become so marked that further heparinization was deemed unnecessary. By the third day the clotting time had returned to values

obtained on admission. The course in the following ten days was one of progressive and almost complete disappearance of all previously described abnormalities of the circulation in the part. A few dilated venules over the right upper anterior thigh remained, and these, too, had disappeared by the thirteenth hospital day. When complete clinical clearing was evident, a venogram, using two injections of 5 c.c. of a 35 per cent Diodrast solution for posteroanterior and lateral films, was performed via a cannula inserted into the right external saphenous vein. The patient was discharged well on the eighteenth day after onset of symptoms. He was seen four months after discharge, at which time he appeared entirely well. Both lower extremities were equal in length and in circumference at several points, and skin temperatures were the same in both extremities. There was not a trace of a superficial venous channel over the abdomen or legs. No abnormalities of the extremities had presented at any time following discharge.



Fig. 1.—Phlebogram, right leg, lateral view. Note absence of deep system, striking number of tortuous collaterals, and deformity of femoral bulb (arrow).

#### COMMENT

Interpretation of phlebograms, even by those very experienced in this technique, is often difficult because of frequent variations in the normal and because of pooling of the injected dye in normally patent veins, depending on speed of injection and actual positioning of the extremity when the exposures are made. Since no mention of phlebography in the age group of this patient could be found in the literature, the problem of interpretation without either normal

or abnormal films for comparison would appear all the more difficult. Despite this, the venogram in this instance shows characteristics of obstruction repeatedly emphasized and agreed upon in authoritative works on the subject.<sup>5-7</sup> Thus, the accompanying illustration shows complete failure of filling of the deep venous system of the leg from a point just below the origin of the common femoral vein, a filling defect at the junction of femoral and saphenous veins (marked by arrow), and finally a striking number of tortuous venous collaterals. These abnormalities in the venogram, together with the clinical picture and course of this infant, leave little doubt as to the primary diagnosis of venous thrombosis.

Although the etiology of venous thrombosis is still not entirely clear, and though there continues to exist considerable disagreement among authorities on the subject, nevertheless certain fundamental conditions necessary to thrombosis are generally admitted.<sup>6-12</sup> These are: first, changes in the blood itself, such as increased coagulability as occurs in thrombocythemia or in severe hemoconcentration; second, changes in the blood flow with slowing and formation of eddies; and third, changes in the vessel wall itself, whether as the result of mechanical or chemical trauma or of infection. The patient described presented at least two of these three major factors, namely, slowing of the venous flow in the lower extremities and unquestionable local injury, both as a consequence of unusually severe pressure exerted in the region where the vessels are quite superficial.

The clinical picture seen on admission to the hospital indicated a much more widespread phenomenon than could be accounted for solely by the presence of an obstructive process in the major venous channels of the leg. Thus, there was probably a large element of contiguous arterial spasm as indicated by the loss of femoral pulsation on the side of the presumed thrombus. In addition, the extremity was definitely cooler than the opposite side, it was cyanotic, and blanching on very slight pressure could be demonstrated. The fact that an area blanched by pressure could restore its circulation rather quickly would indicate incomplete arterial closure by the spasm. The non-pitting edema of the leg suggested some lymph stasis as well as a more diffuse tissue disturbance resulting from impaired arterial and venous circulation with concomitant lowering of temperature of the part.

The condition of very transient mild cyanosis and diminished temperature of the left lower extremity was probably associated with a vasospastic phenomenon related to the pressure exerted in the left inguinal region at the time of the circumcision. This would seem to be analogous to the situation not infrequently arising following femoral puncture in which there is some difficulty in transfixing the vein, with possible excessive trauma to this or to its fellow artery. Cyanosis and lowering of temperature of the leg may then occur, only to subside completely within a few hours of onset. The mechanism of widespread arterial and probable venous spasm which occurred in the right leg in this case might well be compared to the situation in adults in whom lumbar sympathetic block may result in prompt relief of many of the circulatory changes in an extremity which is the site of a venous thrombosis.<sup>16, 17</sup> Reflex phenomena mediated through the network of sympathetic plexuses in the adventitia of veins and of arteries in close proximity to veins may thus result in an area of circulatory embarrassment far from the original site of injury. Lumbar sympathetic block was not felt to be indicated in this instance in view of the rapid improvement after a short period of observation, and because of the truly remarkable and apparently adequate collateral circulation which developed with such great rapidity. Extension of the

thrombus with possible serious embolization was feared, and so heparinization was begun, although not carried beyond a twenty-four-hour period. In retrospect, lumbar sympathetic block as soon as the patient was seen might have been a logical procedure, since much of the circulation of the leg would have been restored rapidly, thereby eliminating at least the factors of continued stasis and deficient nutrition which conceivably might have led to extension of the thrombus. Long-term sequelae of deep venous thrombosis, although frequently seen among adults, could not reasonably be expected to occur in the age group of this patient.

#### SUMMARY

A case of major venous thrombosis in the right lower extremity of a newborn infant is described, with commentary on probable etiology and associated pathologic changes. The diagnosis was confirmed by phlebography.

The author is indebted to Dr. Samuel Karelitz and Dr. Ralph Moloshok of the Mt. Sinai Hospital Pediatric Service for their advice and interest in the study of this case.

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## INTUSSUSCEPTION IN A NEWBORN INFANT

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CASE reports of intussusception occurring at birth, or in the first few days after delivery, are rare in the literature. We wish to present such a case, of interest not only from the standpoint of the immaturity of the infant, but also because of the absence of some of the most important criteria on which to base a diagnosis.

The infant was brought to us on the third day of life with the chief complaint of bleeding from the rectum. The father, who brought the patient to us from some distance, was unable to give any history, and we did not obtain one for twenty-four hours.

This female infant was delivered on the evening of Oct. 20, 1948, by an osteopath in a private hospital. Delivery was without incident, and routine care was given. The following day the baby was put to breast and given a commercial formula. The stools were of normal meconium. That evening a slight blood staining was noted in the meconium; it was noted again at each diaper change throughout the night. By 5:00 A.M. on October 22, the infant was still nursing well and passing blood-stained meconium, but there now occurred an emesis of the feeding, followed by a brown-colored vomitus. The abdomen was not rigid, and no masses could be palpated. Rectal examination was negative. A high enema was ordered. Vitamin K was started, and amino acid was given subcutaneously when fluids were refused by mouth. The attending osteopath examined the abdomen several times throughout the day, and each time the physical findings were essentially negative. At no time was there evidence of pain or discomfort. Slight bleeding from the rectum continued, however, and a local pediatrician was called who suggested that in the absence of obstructive symptoms, the Rh factor was probably at fault.

On entry, the infant was alert, and appeared to be in no distress. Jaundice was evident, and the temperature was 103.4° F. rectally. The abdomen was soft, nontender, and no masses could be palpated. Bowel sounds appeared normal. The cord was healing satisfactorily. There was fresh blood on the diaper, and clots and bright red blood were seen to ooze from the rectum occasionally. The admitting officer believed that he had felt a mass in the rectum, but it had immediately moved upward from his finger and could not be felt again either in the rectum or abdomen.

Vitamin K was injected in the buttocks. Feedings were withheld pending further examination. The Rh of the father and mother were reported as positive. The infant's blood count was as follows: red blood cells, 5,950,000; white blood cells, 12,500; 16 Gm. hemoglobin; bleeding time, 1:53; and coagulation time, 2:15. Surgical and proctologic consultation was requested.

An infant proctoscope was used. The rectal canal admitted the instrument with ease, and it was advanced to an 8 cm. level without difficulty. No abnormalities were noted. At approximately 10 cm. the entire lumen of the canal was occluded by a bluish, congested, shiny mass. No lumen was seen in the mass, and during the course of observation this mass moved upward and disappeared from view. It could not be definitely determined if this mass was the end of an intussuscepted bowel or a rectal polyp on a long pedicle. We were inclined to believe that the latter was correct.

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The infant still showed no distress. Two ounces of formula were now taken by mouth, and somewhat later an additional  $\frac{3}{4}$  ounce was consumed.

Finding it difficult to believe that we were dealing with an intussusception in the absence of clinical signs, we held the infant under observation until morning.

She was then found to be weaker, somewhat dehydrated, and had a slightly bluish discoloration surrounding the navel. The abdomen for the first time showed slight resistance, but still no masses were palpable. The diaper contained about 2 to 3 c.c. of dark blood, and there had been no stool passage. Projectile emesis of a rather large amount of greenish stained vomitus occurred.

Surgery was now believed to be imperative, and the child was fortified with subcutaneous fluids and a small whole blood transfusion. X-ray studies of the colon had been unsatisfactory, as the barium had been expelled almost as soon as injected. However, a flat plate of the abdomen showed considerable air under both leaves of the diaphragm. There was definite dilatation of some of the loops of the small bowel.

The peritoneal cavity was exposed through a lower left rectus incision and revealed several ounces of cloudy fluid speckled with barium. The small bowel was moderately distended. An elongated mass was palpable from the rectosigmoid to the splenic flexure. A 2.5 cm. by 1 cm. perforation was seen at the sigmoidal flexure. Telescopic colon was seen through the perforation, and its distal portion extended to the rectosigmoid juncture. This was brought up through the perforation and proved to be the cecum, appendix, and a portion of the ileum. The complete intussusception was then reduced. The cecum, the entire ascending colon, and 4 cm. of the ileum was gangrenous. The right half of the colon and 6 cm. of ileum were resected, and an end-to-side anastomosis of the ileum and transverse colon was done. Because of the unusually large perforation and the presence of several 1 cm. by 1 cm. necrotic areas at the lower one-third of the descending colon, it was necessary to resect 8 cm. of the left colon and perform an end-to-end anastomosis. A mixture of penicillin and sulfathiazole powder was instilled in the peritoneal cavity, and the wound was closed in layers. At the conclusion of the operation the respirations became labored and finally ceased. The pulse was still perceptible, and despite positive pressure, oxygen administration, artificial respirations, and intravenous injections of a stimulant, the patient expired.

The pathologic report does not throw much new light upon the situation, except that there was massive hemorrhage into the wall of the specimen around the region of the ileocecal valve, and no lumen could be identified grossly there.

#### COMMENT

Reports of intussusception in the neonatal period are not completely new in the literature, as there have been thirteen reported as having occurred in the first six days of life. Of particular interest to us are those which have occurred in the first two days postdelivery. Lewis<sup>4</sup> lists the first case of jejunal intussusception occurring in a one-day-old infant. Perrin<sup>5</sup> published a monograph based on 400 cases, the youngest patient being one day old. Jeffrey<sup>2</sup> reported the third case in a one-day-old infant. Gelston<sup>1</sup> cites the case of the baby who passed elots by rectum on the evening of the second day, vomited on the third day, and died of intussusception on the fifth day without surgery. To make our record complete Tweedy<sup>6</sup> mentions the newborn infant who had hemorrhage from the bowel on the second day and died on the third day of an intussuscepted bowel.

It is our feeling that our infant developed this condition during the first day of the postdelivery period. Ladd<sup>3</sup> states that the blood usually appears at the fourth to twelfth hour after intussusception occurs.

In this case we were dealing with an infant with massive gangrene, perforation, and peritonitis, and yet who showed no sign of cramping, distention, rigidity, or distress, which usually attend such a condition. We wish to point out that such diagnostic criteria may be absent in the newborn infant.

#### SUMMARY

The sixth case of intussusception occurring in the one- to two-day-old infant is reported. It is of especial interest because the usual diagnostic criteria were absent even though gangrene, perforation, and peritonitis were present.

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# Clinical Conference

CONFERENCE AT THE CHILDREN'S HOSPITAL OF  
SAN FRANCISCO, JAN. 4, 1949

PEDIATRIC DEPARTMENT

## Case 1. Xanthomatosis

H. E. THELANDER.—The case presented today is of interest because at the age of 6 months when first seen on Jan. 19, 1947, the patient presented a picture of unmistakable skin xanthomatosis combined with marked hepatosplenomegaly and a blood picture not unlike a leucemia. The history revealed that at the age of 3 months a small red bump resembling a mosquito bite first appeared on the forehead. It began to enlarge and turn yellow, finally reaching the stationary size of a small pea. Further small masses developed on the top of the head about two months later. These evolved similarly but in general were smaller in size. There were no other presenting symptoms.

There was no history of abnormality in birth, development, or feeding; there were no previous diseases other than three mild upper respiratory infections; and there was no similar condition in the family.

On examination the temperature, pulse, and respirations were normal. The skin showed typical xanthomata over the scalp. There were numerous lesions, varying from a pinhead up to a split pea in size. There were small areas of brownish discoloration over the skin of the forehead. The skin of the remainder of the body was free of lesions. There was a moderate pallor. The head was normal in size, with fontanels not unduly large. The eyes were rather widely spaced and prominent. Throat, chest, heart, and lungs were negative. The spleen was enlarged, reaching midway to the iliac crest. The liver extended 3 fingerbreadths below the right costal margin. There was no tenderness. Genitalia, extremities, and neurological examination were negative. The lymph nodes were moderately enlarged, discrete, and nontender.

Complete blood count revealed: hemoglobin, 6.2 Gm.; red blood cells, 3.2 million; white blood cells, 45,700. The differential count was polymorphonuclears, 42; nonfilamented, 31.5; eosinophiles, 2.5; basophiles, 5; lymphocytes, 47; monocytes, 3.5; unclassified, 3; blast cells, 1.5. Examination of urine revealed only an occasional white blood cell. Sedimentation rate 3 mm. per hour. Blood chemistry was: blood total cholesterol 101.6 mg. per cent; serum phosphorus, 5.1 mg. per cent; alkaline phosphatase, 2.3 Bodansky units; cephalin flocculation, negative. Kolmer and Kahn negative. Sternal marrow aspiration showed promyelocytes, 0.8 per cent; and of myelocytes, neutrophiles, 6.4 per cent, eosinophiles 5.0 per cent, polymorphonuclears nonfilamented 24.0 per cent and filamented 1.8 per cent. Plasmacytes were 0.4, promonocytes 2.8, monocytes 18.4, pro-erythroblasts 0.8, erythroblasts 7.2, megakaryocytes 0.4, and histiocytes 1.8.

X-ray studies reported the skull and chest negative; the long bones showed "Non-reactive periosteal calcification along the shafts of the large long bones."

Biopsy of the scalp lesion was reported as a "granulomatous lesion with lipid holding cells."

The patient was placed on a low cholesterol diet. Supplementary iron and brewers' yeast was given.

On April 11, 1947, the patient was rehospitalized because of an acute upper respiratory infection accompanied by fever to 104° F., cough, and cervical adenitis. Throat culture revealed Beta hemolytic streptococcus. The patient became afebrile in four days with penicillin and supportive therapy. A restudy of the general systemic disease at this time revealed hemoglobin 9.3 Gm., red blood cells 3.98 million, white blood cells 36,350, polymorphonuclears 39, non-filamented 29, lymphocytes 52, unclassified 11. Skull x-rays revealed no significant changes. Skeletal x-rays revealed "cortical hyperostosis of the large long bones." Biopsy report on an axillary lymph node and scalp lesion was "reticulosis with lipid storage." The lipid was not identified but studies showed that it was not neutral fat.

On May 5, 1947, the patient entered the hospital for a blood transfusion. In the interval from May, 1947, to September, 1947, a total x-ray radiation dose of 400 R. was delivered over the posterior and anterior trunk and 300 R. to the scalp. New cutaneous lesions began to appear on the neck and thorax; however, the general condition seemed improved. The liver and spleen decreased slightly in size. From November, 1947, to May, 1948, there were frequent upper respiratory infections and fever. There had been several episodes of rather severe epistaxis. A moderate anemia had gradually developed. On March 3, 1948, hemoglobin was 54; red blood cells, 2.78 million; white blood cells, 15,400; polymorphonuclears 47; eosinophiles, 3; basophiles, 0; lymphocytes, 44; monocytes, 6. Although development was retarded, the baby was now able to walk and say a few words. The mental age appeared to be about one year. Physical examination revealed additional significant findings. There was moderate protrusion of the eyes with slight bossing of the frontal bones (head circumference 20 1/8 inches). The cervical lymph nodes were somewhat larger than previously. The liver was enlarged to 6 cm. below the right costal margin, the spleen was enlarged to 6 cm. below the left costal margin. There was a spadelike appearance to the hands and marked bilateral calcaneovalgus of the feet. Complete blood count after transfusion revealed a hemoglobin of 10.5 Gm.; red blood cells 3.77 million; white blood cells, 23,250; polymorphonuclears, 48; filamented 34; non-filamented, 14; eosinophiles, 2; basophiles, 1; lymphocytes, 30; plasmaocytes 10, metamyelocytes, 7; myelocytes, 2. X-ray examination showed that since previous examination on April 22, 1947 "the right parietal bone had developed faint striations, increased density, and apparent mottled areas of decalcification." There was "possible elevation of the orbital roof but there was no evidence of bone destruction."

The fourth hospitalization occurred Aug. 31, 1948. About two months before this entry anemia became more marked. Further small transfusions were given and frequent febrile episodes were treated with penicillin. One week before entry further x-ray therapy was directed to the liver and spleen. Physical examination revealed a marked pallor, prominence of the eyes, and skin lesions present on the back and buttocks. The abdomen was markedly distended

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with the liver and spleen each palpated 12 cm. below the midcostal margins. Both were firm and nontender. The fingers appeared noticeably shortened.

Complete blood count showed: hemoglobin 10.7 Gm.; red blood cells, 3.42 million; white blood cells, 17,350; polymorphonuclear, 18. Lymphocytes were 81; monocytes, 2; platelets, 160,000; packed cell volume, 37 per cent; sedimentation rate, 18. Blood cholesterol total was 69.5 mg. per cent, free, 50 mg. per cent.

Treatment consisted of transfusions, penicillin, and other supportive measures. However, the baby remained febrile and became weaker throughout hospitalization. For the last three weeks there was a marked susceptibility to cutaneous infections. A marked spontaneous drop in white blood cells from 17,000 to 3,000 occurred ten days before death, and platelets dropped to 60,000. A week before death 7 doses of aminopterin 0.5 mg. was administered.

A few days before death a progressive anal cellulitis appeared. The patient died on Sept. 23, 1948, at 26 months of age.

J. T. CRANE.—This infant, upon examination, was quite emaciated; the head appeared to be somewhat prominent, that is, the cranial vault seemed prominent as contrasted to the facial bones. The eyes were slightly protruding, though it was not definitely established that exophthalmos was present. There was xanthomatous lesions varying from a few millimeters to 12 cm. in diameter over the scalp, neck, and thorax. In addition, there were small vesicular lesions of an inflammatory nature over the body. The abdomen was greatly distended due to the enlarged liver and spleen.

Of the internal organs, the liver and the spleen were the most remarkable. The liver weighed 1,400 grams, which is about the normal size for an adult. It was finely mottled; it had rounded edges and was quite firm in consistency. The spleen was likewise enlarged, weighing 225 grams. It, too, was firm and showed, upon close inspection, accentuation of the trabeculae and milium foci.

The lungs were striking in so far that they contained in the subpleural regions yellow nodules, often flat but occasionally spherical.

Examination of the heart, kidneys, and gastrointestinal tracts showed yellowish nodules in the subepicardial and endocardial regions of the heart, in the subpelvic regions of the kidneys, and in the submucosal areas of the gastrointestinal tract.

The lymph nodes were of two types. Those about the pancreas were large, up to 3 cm. in diameter, somewhat red, and fleshy. Other nodes, those of the cervical region and about the lower abdominal aorta, were somewhat yellow in color and firm in consistency.

The brain was of normal size and showed grossly what was thought to be areas of increased firmness throughout the cortex. However, this finding was not substantiated by microscopic examination.

The skull showed definite punched-out areas about  $\frac{1}{4}$  to  $\frac{1}{2}$  cm. in diameter in both the parietal and frontal bones. There were also yellowish depositions in the medullary portions of the base of the frontal and the sphenoid bones.

The periorbital fat appeared slightly increased and somewhat edematous, which probably accounted for the slight prominence of the eyes. There were no bony defects to account for the exophthalmos.

Microscopic examination of the liver revealed the periportal connective tissue increased in amount. The increased cellularity was due to accumulations of histiocytes, a certain amount of fibroblasts with collagen deposition, and a few inflammatory cells, some of which were eosinophiles. There were a few free megakaryocytes in the sinusoids of the liver. The special stains showed no appreciable amount of lipid deposition in the liver.

The spleen showed an increase in cellularity both intra- and intersinusoidal. The intersinusoidal cells consisted chiefly of histiocytes. These cells showed no evidence of lipid storage. The intersinusoidal cells consisted of histiocytes, megakaryocytes, occasional myelocytes, and normoblasts. Throughout the milary areas that we saw grossly were accumulations of histiocytes.

Sections of the lymph nodes showing a yellow color about the periphery revealed that many of the cells with clear cytoplasm were histiocytes; through the cortex of the gland was found moderate dilatation of the sinusoids. These sinusoids were filled with blood and blood-forming cells. Megakaryocytes were common throughout.

Sections of the lung through the yellow plaques found these to be composed of diffuse sheets of closely packed histiocytes, some of which contained clear cytoplasm. Examination of such lesions under polarized light definitely established the fact that there was cholesterol. However, there was also a moderate amount of lipids present, as well as we could ascertain by our staining technique. So the lipid characteristic of this disease was probably a mixed one. It was not a pure cholesterol deposition.

All the bone marrow that was examined showed involvement. There was no normal bone marrow present. This involvement was quite characteristic. In areas of considerable cellularity, the cells again were histiocytes. Occasionally they contained considerable amounts of lipid material. Other areas of bone marrow showed a fibrosis, so evidently these histiocytes were not only differentiating toward a lipid storage type of cell or actually a macrophage, but they also apparently had the potentiality to become fibroblasts.

In some areas there was complete replacement of bone marrow by reticulo-endothelial cells.

J. T. LANMAN.—There are two aspects to this case which are of more than passing interest. The first of these relates to the consistent finding of abnormal cells in the circulating blood during the two years that this case was followed and detailed hematologic reports were made. Although these cells are variously described by different observers, there seems little doubt but that the essential character of the differential remained unchanged throughout the course of the illness. On the other hand, the total white count showed a persistent fall from the striking leucocytosis on the first examination to the leucopenia observed on the last admission. To my limited knowledge this type of blood change has not been reported in the literature in association with xanthomatosis, although the finding of certain other bizarre abnormal cells in the peripheral blood is, of course, not unusual, and in Niemann-Pick disease it occurs to such an extent that the large fragiliocytic cells which are released into the circulating blood are said to block the pulmonary capillaries, where they are filtered out, presumably on the basis of size. It was our impression at the laboratory that this picture was

consistent with leucemia and that the trial of aminopterin might afford some benefit, although on the whole our experience with this drug has not been encouraging. It was fortunate in this case that a blood count was done immediately before the beginning of aminopterin therapy for, in this instance, although the results of this blood count were not known until after therapy was instituted, it marked the beginning of a definite and striking fall in the white count which, because of its onset definitely before the beginning of aminopterin therapy, must in all likelihood be ascribed to the spontaneous course of the disease. Because of the profound leucopenia, aminopterin was quickly discontinued and not restarted until two days before death, at which time the leucopenia had somewhat abated. There has been considerable discussion as to whether these cells in the blood might represent circulating histiocytes. At our present state of knowledge this appears to me to be a somewhat fruitless argument, but at the laboratory where our smears are studied by the supravital technique it was our impression that the cells were of the lymphocytic series although somewhat bizarre in appearance. There would appear to be no particular reason why, in a disease of this nature which is characterized by extensive reticuloendothelial hyperplasia, occasional cells of an unusual nature should find their way into the circulating blood.

A second feature of considerable interest in this case are the transitional characteristics between the various types of xanthomatosis which it represents. The evolution of thinking in regard to this group of diseases during the past forty years is of extreme interest. Hand was the first to describe a pathologic report of the case, representing what is now known as Hand-Schüller-Christian's disease. In his original report it was his impression that the most likely diagnosis was tuberculosis, although certain atypical features of the case led him to suspect his own diagnosis. Some years later Schüller described the x-ray changes which are characteristic of the disease and shortly thereafter Christian recognized the symptom triad from lesions in the bone, exophthalmos, and diabetes insipidus. It is now well recognized that these findings and symptoms are dependent purely on the chance location of the xanthomatous infiltration and that in any given case any one or perhaps all of this triad may be missing.

At about the same time a disease entity now known as the Letterer-Siwe's disease was first being described, pathologically by Letterer and later clinically by Siwe. The clinical entity described was one of hepatosplenomegaly and generalized glandular enlargement with a hemorrhagic diathesis, a progressive and invariably fatal course, and on pathologic examination an extensive, generalized proliferation of the reticuloendothelial tissues. In contrast to certain other forms of xanthomatosis it was thought that this disease was both nonhereditary and nonfamilial. Although on superficial examination it might appear that there was little in common between these two diseases, it was pointed out by Waldron in 1940 that the differences which did exist were no more extensive than might be encountered in any single disease entity with its varying manifestations. It was his impression that so-called Letterer-Siwe's disease presented a more fulminating disease which, in its more chronic form, was clinically recognized as the Schüller-Christian syndrome. In support of his contention he cited a few cases which appeared to be transitional between the two forms of the

disease. It was also in 1940 that Liehtenstein and Jaffe first described what they thought to be a new disease entity and for which they proposed the name eosinophilic granuloma of bone. These were usually solitary lesions in which the x-ray picture was confused with certain other entities as, for example, giant cell tumor of bone which on pathologic examination showed a bizarre picture in which the infiltration with the eosinophiles was the most striking characteristic, but in addition to the eosinophilia a highly pleomorphic picture was presented. Because many of the conditions with which this picture was confused were highly malignant, the benign prognosis of the eosinophilic granuloma was the more striking. It was rapidly pointed out, however, by Farber and others, that this so-called "new disease entity" was in actual fact not a new one but it had been recognized previously and, in the opinion of Farber, represented but one stage of the osseous lesions of the Schüller-Christian syndrome. The numerous transitional cases between typically eosinophilic granuloma of the bone and the Schüller-Christian syndrome, and the frequent pathologic impossibility of distinguishing the two conditions rapidly led to a degree of agreement that the diseases were at least very closely related. However, it is my impression that it is still open to question whether or not in a given case of Schüller-Christian's disease with bone lesions there is anything like an orderly progression of the pathologic picture which at some stage or other will represent the picture of eosinophilic granuloma of bone; or, conversely, whether eosinophilic granuloma of bone will heal by resolution or through the stages of connective tissue scarring which are more characteristic of the Schüller-Christian syndrome. In the main, however, there has been a great simplification of thinking with regard to various disease entities which fall under the heading of xanthomatosis, and indeed it is not clear that xanthomatosis is a proper name for this group of diseases at all, inasmuch as the current thinking about the group seems to indicate that the fat storage is purely facilitative. The case which we are discussing fairly clearly represents the transitional stage between Letterer-Siwe's disease and typical Schüller-Christian's although it is striking that the first manifestation of the disease was the xanthomatous infiltration of the skin of the scalp. It is also striking that this infiltration occurred at a very early age so that it is certainly clear that extreme chronicity is not necessary to the appearance of xanthomatous lesions in Schüller-Christian's disease. It may also indicate that more than a simple time factor is involved in determining whether a specific case will or will not show fatty infiltration.

DR. PEARL SMITH—There are a number of confusing things about this case. The lesions were so brilliantly pigmented that I fully expected to find a rather heavy deposit of cholesterol. I think there is some question as to whether the cells in the blood really should be called monocytes. Where there is as much proliferation of reticuloendothelial cells as you can see in this case (and I thought definitely some of them seemed to be rounding up and separating) they might easily get in the blood stream.

DR. CRANE—My understanding was that the lesions were not yellow at first but like a mosquito bite.



DR. THELANDER.—The lesions varied from time to time. Sometimes they were distended, shiny, and intensely yellow, and at other times they were flattened out and looked almost like crystals of yellow material under the skin; as they faded they would assume a reddish hue. Likewise the new ones when they first appeared often looked like red hives that would gradually become more yellow.

DR. E. B. SHAW.—At about the same time as this child was seen we had several newborn or young infants who had a number of xanthomatous lesions on the scalp and body. It does not take long for a lesion to develop from a size you do not notice to one that is quite obvious. There was little difference in these completely benign lesions from those early present in this case.

DR. THELANDER.—The liver and spleen were sent to the university laboratory for chemical studies but this report is not yet available. The case presented was a most interesting and instructive case to follow and study. The patient has shown some manifestation of practically every type of case grouped under the heading of xanthomatosis from reticuloendotheliosis at one end of the spectrum through Letterer-Siwe, Hand-Schüller-Christian to monocytic leucemia on the other. The two years showed little evidence of progression from one phase to another and it is likely that such a concept of xanthomatosis is erroneous.

### Case 2. Pertussis in an Immunized Infant

DR. EDWARD B. SHAW.—We now consider a problem which is becoming a rarity in private practice: a case of pertussis in a 22-month-old infant who had been immunized previously. This brings up the problem of immunization, its effectiveness, the age at which immunization is preferable, and finally, the treatment of the acute symptoms. Dr. Randolph, the interne, will present this case.

DR. RANDOLPH.—E. D., a 22-month-old white female infant, was admitted to the communicable disease ward Jan. 19, 1949, with a complaint of paroxysmal cough for one month. This child had been well previously, and the cough was initiated with a slight coryza, with a fever of 38.4° C. on only one occasion. For a period of three weeks before hospital entry the cough had become progressively worse, a characteristic whoop developed, and there was attendant vomiting.

This infant was immunized during the period of July 12 to Aug. 15, 1947, aged 3 to 4 months, by a physician in a Southeastern state, using three injections of a saline suspension of killed *Hemophilus pertussis* totaling 100 billion organisms.

There was a convincing history of exposure to whooping cough in an urban housing development.

Physical examination at entry showed nothing beyond the evidences of continued whooping cough in an infant. The child was exhausted, pale, and had obviously lost considerable weight. The paroxysms of coughing were unmistakably those of pertussis, and were accompanied by a loud whoop and considerable cyanosis. There were no evidences of complication apart from the exhaustion and malnutrition.

Blood count showed hemoglobin 13.0 Gm.; red blood cells 4.7 million; white blood cells 14,700; polymorphonuclears 59 per cent (8 nonfilamented), lymphocytes 34 per cent, eosinophiles 1 per cent. The sedimentation rate was normal, the urine was negative. Throat culture contained a few gram-negative rods which were not identified as *H. pertussis*; a conventional cough plate was also negative for *H. pertussis*.

The child had received on the second and third day before admission 20,000 units of Antipertussis Endotoxin—a rabbit serum product provided by Wyeth. In the hospital the infant was treated with streptomycin aerosol, 50 mg. every two and one-half hours. Paroxysms increased in frequency and severity over the first four hospital days. On the second hospital day a few scattered rhonchi and musical râles were heard throughout the chest; at this time the chest film showed no evidence of consolidation. On the third hospital day one-half cubic centimeter of pertussis vaccine (20 billion organisms) was given intramuscularly. By the fifth hospital day the paroxysms definitely decreased. On the fifth day she was discharged home greatly improved, and the improvement has continued at home.

Although bacterial confirmation was lacking, there seemed to be no doubt of the diagnosis. Evaluation of therapy was difficult. The anti-endotoxin administered before entry seemed not to be of benefit, although this may have contributed to the rapid improvement in the hospital. Streptomycin aerosol was not spectacularly effective. The recall injection of pertussis vaccine was succeeded by rapid improvement, although this may have been coincidental. Final improvement may have depended upon nursing care, one or another of the therapeutic agents, or simply the effect of time.

DR. WILLIAM J. KERR.—In addition to attempted specific therapy this child received various antispasmodic drugs but the effect of these was equally hard to evaluate. Oxygen was used only as a means of administering the streptomycin aerosol.

DR. SHAW.—We have two visitors who are interested in the question of immunization and therapy brought up by this case. Dr. Deamer, would you like to open this discussion?

DR. W. C. DEAMER.—The point which Dr. Kerr suggested I comment on particularly was that of the efficacy of early immunization to pertussis. I am glad to have the opportunity to review the evidence for and against immunizing infants with pertussis vaccine before the customary six-month age period. I have personally been loath to do this, as I had the impression that there was fairly good evidence that immune mechanisms were not as efficient in the very young animal as they were later on. This impression has been strengthened by my review of the evidence.

To begin with, it may be well to point out that all antigens are not equally antigenic and that were we discussing diphtheria or tetanus toxoid as an antigen, the score might be different. These, by comparison with pertussis vaccine, are considerably better antigens. Some of the early failures of pertussis immunization relate to its poor antigenic qualities. The presently recommended high

doses of pertussis vaccine also attest this fact. Since we are dealing with one handicap in this respect, the existence of another possible handicap becomes of especial concern, lest the double handicap compound the failures of immunization which we will encounter.

The evidence that the immune mechanism in the very young animal is not comparable to that of the older animal is varied. Freund and Baumgartner demonstrated in several species of animals and with several different bacterial and other antigens a difference in favor of the older animal in quantitative antibody response. There is evidence in the German literature that newborn infants respond less well to typhoid vaccine than do adults. French authors have shown that older children respond to diphtheria toxoid better than younger children. The development of natural antibodies such as isoagglutinins also points in the same direction. They are not usually present under one month nor do they reach adult levels until 2 years of age. There are a good many additional articles indicating a similar improvement in antibody production with age. These include a wide variety of antigens and several species of animals including the human being.

On yet another somewhat theoretical ground, one might expect better antibody response in the older child than is found in the younger child. Although the young infant usually has a high serum globulin level, the gamma fraction decreases progressively after birth. We know that many immune antibodies are carried in this gamma fraction.

While the above comments do not necessarily constitute a complete indictment against early immunization with pertussis vaccine, they certainly form a challenging argument against its complete acceptance. The evidence would seem to be against very young infants giving a very good response. Here we are likely to fall into a battle of words, as the question naturally arises as to how good the response must be, and this cannot be answered categorically. It may be well to point out how extremely variable the response to pertussis vaccine and other antigens is. In a study of tetanus toxoid several years ago we obtained over one hundredfold variation in antitoxin formation in a group of 150 infants given the same antigen in the same manner. If the group had been larger the range of variation would undoubtedly have been larger also. This variability of antibody response has been demonstrated right down the line and includes pertussis vaccine. The question then is not how many in a group respond exceptionally well, but how large the group of poor responders is, for it is among them that the failures will occur. The recent article of di Sant' Agnese on the immunization of newborn infants indicates to me that the group of poor responders to pertussis vaccine among the newborn infants is too large. Forty-six per cent were without a "protective" titer of pertussis serum agglutinins one month after the last of three injections of a triple vaccine. In a comparable group of older infants this author had previously found only fifteen per cent without a protective titer. The evidence against the relative response of the younger infant is clear even if we disagree as to what constitutes a protective titer.

Thank you, Dr. Shaw. I shall be interested in hearing your opinion and that of Dr. Miller on this interesting question.

DR. SHAW.—Apart from the effect of age of immunization there is also the question of variation in antigenicity of vaccine. Dr. Bower told me last week in Los Angeles that he had observed a series of failures in pertussis immunization which he had traced to a single vaccine. He stated that this particular preparation proved to be a very poor antigen, was a decidedly rough strain and not a Phase 1 organism. It was his opinion that such failures would not infrequently, and perhaps unavoidably, be encountered. Dr. Miller, do you want to carry on?

DR. J. J. MILLER.—This youngster provides an excellent example of the failure to protect with a dose of 100 billion saline-suspended *H. pertussis*. Four reasons why this child might not have been protected are: she might have been too young; she might have been a congenitally poor reactor; the lot of vaccine employed might not have been potent, for there has been no certain way to standardize the potency of vaccine; and the fact that the vaccine used was suspended in saline, not precipitated with an adsorbent. The evidence that infants under 6 months of age can be protected with whooping cough vaccine rests first and foremost on the field study of Wallace Sako and his collaborators in the United States Public Health Service in New Orleans. They injected a total of 40 billion alum-precipitated *H. pertussis* in three divided doses at monthly intervals, beginning in the second month of life. It was possible to follow almost 2,000 injected infants and a like number of controls for a period of one to two years. During this time the secondary attack rate following familial exposure was over 80 per cent in the control group whereas it was less than 20 per cent in the inoculated group. This statistically significant evidence of protection was in contrast to earlier reports on the protective efficacy of vaccine at such an early age. Incidentally, these workers were able to demonstrate that clinical protection was associated in these infants with the carriage of serum agglutinins in high titer (that is, 1:320 or more), a finding previously reported from our clinic.

The remaining evidence in favor of early immunization is supportive but indirect. There has been no other field study reported. The supporting evidence consists of a report by Dr. Halper of Texas, in which was employed the same product at the same age as Sako. The immune response was gauged by serum agglutinin estimations and the development of antibody in the skin. To this may be added the report of di Sant'Agnese and some work that we have done at Stanford during the past four years.

In our experience 40 billion alum-precipitated *H. pertussis* will induce and maintain for one year levels of serum agglutinin consonant with immunity in 60 per cent of infants. This does not mean that only 60 per cent of the infants were protected. The presence of agglutinins in low titer following vaccine and even the absence of agglutinins does not imply susceptibility. Sako found that in vaccinated infants with titers below the critical level of 1:320, the secondary attack rate varied inversely with the titer and reached a maximum of 33 per cent in those infants carrying no agglutinins. Thus it is fair to estimate, I believe, that the precipitated vaccine we employed protected 60 per cent of the infants plus one-half of the remainder, or a total of 80 per cent.

There is, I think, adequate evidence to say that the ability to immunize varies directly with age. It is a question of what percentage of individuals you can

immunize at a certain age and whether you can immunize enough to make it practicable. There will always be some individuals whom you cannot protect regardless of age. It is our belief, based on the report of Sako and supportive evidence that I have mentioned, that it is practicable and advisable to attempt immunization beginning at 4 to 8 weeks of age, providing a precipitated or adsorbed product is used. There is considerable evidence that such adsorbed antigens are more effective immunizing agents than saline-suspended vaccine.

We have seen children who received saline-suspended vaccine under 6 months of age who contracted pertussis, just like your patient. We have not yet seen infants who had received precipitated vaccine develop pertussis, but of course we will see some sooner or later.

DR. PATRICIA CLARK.—Dr. Miller, I should like to ask your opinion regarding the effectiveness of a recall dose of vaccine. This child unfortunately received no booster dose. I saw her a short time before the onset and recommended a booster dose, but this was deferred because the child had a slight upper respiratory infection. Can you compare the protection in those who have had only immunization in infancy with those who have had one or more booster injections during the next few years?

DR. MILLER.—That depends on the three factors: type of vaccine used, whether it was precipitated or adsorbed; the total dose; and the efficacy of the immunity factor of that individual. Using saline-suspended vaccine in a total dose of 80 billion, reports from widely different sources have indicated that secondary attack rates following familial exposure vary from about 10 per cent to 30 per cent. I think one can conservatively say that in an older child these injections will protect two out of three children exposed in the home and four out of five children exposed in the school or elsewhere.

DR. BAUMANN.—Dr. Miller, how would you feel about using a combined vaccine which is not, as I gather, completely precipitated but only partly so, such as Tri-immunal with a lesser concentration?

DR. MILLER.—We use Tri-immunal, alum-precipitated occasionally. I think it is good. However, the total dose of *H. pertussis* in the recommended total volume of  $1\frac{1}{2}$  c.c. is only 30 billion. I believe that is inadequate. I think you ought to give at least 40 billion or, if you are using a saline product, at least 80 billion.

I would like to comment on Dr. Shaw's remark. I think there may always be isolated lots of vaccines that are not effective. The manufacturers have no accurate means of assaying potency. By and large, if recently isolated strains are used, chances are you will get a good antigen.

DR. SHAW.—It will be interesting to know from those present how many failures have been encountered in private practice. Dr. Yeazell, how many have you seen?

DR. YEAZELL.—I have seen just two. One of these was a child of 6 years who had been immunized in infancy and had had no boosters. The second was an infant of less than a year of age who was immunized in the newborn infant nursery at Stanford.

DR. MILLER.—We had several hundred youngsters in which immunization was started in the nursery with saline-suspended material, and I feel sure that very few, if any, of these infants were protected. Both the age and the product were factors. I doubt if you can attempt immunization under one month to advantage. I do not believe that Dr. Sako is correct when he makes the statement that age does not make any difference.

DR. SHAW.—Immunity is, after all, more or less of an acquired skill. As age advances past infancy the capacity of the tissues to respond to vaccine stimulation improves. I think the point made by Dr. Miller about the use of adsorbed agents is very important. It does make a difference whether saline suspension, precipitated, or adsorbed agents are used. Is that a matter of particle size, Dr. Miller?

DR. MILLER.—I assume it is because adsorbed antigens are released more slowly and the stimulus is more prolonged.

DR. SHAW.—It does increase the particle size, however, and in general this is advantageous.

DR. MILLER.—I do not know.

DR. SHAW.—How about other failures in private practice?

DR. THOMAS CORNWALL.—I do not remember having seen any failures. Pertussis seems to be practically nonexistent in my practice.

DR. DEAMER.—I recall two, Dr. Shaw, one proved by culture. He had presumably been adequately immunized with three doses of vaccine totaling 80 billion organisms. The interval since the last injection was almost two years. The other case was a child who should have gotten three but had only two injections in the basic immunization. I can remember just the two failures.

DR. GELSTON.—I have seen only one failure of protection in which I do not recall the exact method or spacing of immunization. I do not immunize early but prefer to begin at 8 months of age.

DR. DEAMER.—What has been your experience, Dr. Shaw?

DR. SHAW.—I can recall only a single failure among those whom I have immunized and followed subsequently. This child was one whom I referred to an eastern colleague, an old friend in Boston, who was at the time opposed to the use of vaccine. He promptly wrote me to say that ironically enough the child had arrived having his first paroxysm of whooping cough.

I believe that the children who are immunized in private practice and continue under periodic observation by the pediatrician constitute a *de luxe* group with respect to the effectiveness of vaccination. In many respects such a group is far better protected than those who are immunized by public health agencies and similar institutions. By and large, these children are good subjects for immunization by virtue of their better general health, good nutrition, and, to some extent, less frequent opportunity for exposure. Protection is greatly augmented by the fact that contacts with the patient are also usually immunized,

so that the child profits not only from his own immunity but from the fact that he has so little opportunity for exposure to the disease. It is not necessary to carry out 100 per cent immunization in a population in order to give a high degree of protection to a community. The same thing is, of course, true of diphtheria and other forms of immunization.

As the immunization rate rises in the infant's environment, he enjoys progressively better protection from exposure. One may thus consider the advisability of deferring immunization in private practice until a time when the response is more unfailingly reliable. Some slight dangers have been pointed out by reported experience and these dangers of immunization would seem to be accentuated in early infancy.

DR. CLARK.—The two older children in the family of this infant evidently had whooping cough. They were sent home from school with this suspicion and the mother was provided with cough plates by the Board of Health in an effort to establish the diagnosis. Somewhat amusingly, she exposed the cough plates, did not return them for examination during the next forty-eight hours, and during this period there was such a profusion of bacterial growth on the plates that the mother was sure that the children had some lurid infection, perhaps bubonic plague, refused to submit the plates for examination, and returned the other children to school to spread the disease further.

DR. ALICE POTTER.—I have had no failures of immunization which I have observed in my own practice.

DR. GRACE GOEBEL.—I can recall one case, Dr. Shaw, in a 7-year-old child who was immunized in infancy and had had no intervening immunization.

DR. ANN BRADY.—I have one patient at the present time who is 9 years old who is supposed to have had initial immunization in infancy and a series of twelve booster shots given by the Navy. The diagnosis of pertussis accordingly seems as improbable as the number of booster doses but the mother insists that the child has a typical whoop. I suppose we must consider parapertussis.

DR. SHAW.—If we regard immunization as an acquired skill, a sort of activity which must be learned by the tissues; we must still remember that there are some who just cannot learn and there are some who never succeed in developing immunity.

DR. FRANZ BAUMANN.—In regard to a 4-year-old child who had whooping cough, the question came up as to whether one should administer pertussis vaccine along with passive immunization with hyperimmune serum. Is there any evidence to show that such a course affects the disease?

DR. DEAMER.—I do not know but I would be very surprised if it were not at least partially efficacious. An analogy is the proved anamnestic response of an individual previously immunized with tetanus toxoid who is given tetanus toxoid and tetanus antitoxin simultaneously.

DR. SHAW.—Do you have any comment, Dr. Miller?

DR. MILLER.—No, I am convinced that antigen *therapy* is of no value.

DR. DEAMER.—Even in the previously immunized individual?

DR. MILLER.—That would be a booster. I was referring to the use of antigen injections in the treatment of cases in noninoculated children.

DR. SHAW.—Our experience has certainly been most dismal in the use of any antigen against pertussis or the treatment of those not previously immunized. In this particular case we decided to employ a recall injection because of the previous immunization. That the child began to improve about this time probably has no critical significance.

DR. GELSTON.—I would like to know how long we should keep up booster injections, how many there should be, and at what intervals they should be given.

DR. SHAW.—My own practice is to give a booster about two years after beginning immunization at 6 months of age and to give another one at about  $3\frac{1}{2}$  years of age. I find a good many children come to me with instructions that they be given annual boosters. This makes the periodic visit to the doctor rather a trial. What do you think about this? We will ask our experts.

DR. MILLER.—I think you are right. A booster two years after the original course and another one at 6 years of age should be sufficient. I would be inclined to give another one when the child enters high school, having seen some cases in high school youngsters.

DR. SHAW.—Do you not think that the precipitated vaccine is better for the recall injection?

DR. MILLER.—I do not know. We have always used saline-suspended vaccine and found this satisfactory.

DR. SHAW.—The principal use which I make of triple vaccine is for recall injections because I usually divide immunization against pertussis from slightly later immunization against diphtheria and tetanus.

DR. GELSTON.—Is there any reason why rabbit serum was used for treatment in this case rather than hyperimmune human gamma globulin?

DR. SHAW.—The only reason was because we have a small supply of this product on which we are running an experimental study and we have had a very few cases on which to try it.

DR. DEAMER.—I have been very favorably impressed with the Cutter hyperimmune product, so favorably impressed with it I have never gone on to use anything else, but the total number of cases in which I have used it has been quite small. One interesting thing we might look toward in the future is the possible use of polymyxin. I know that in one case in which it was used the improvement was marked. On another it was not as dramatic.

DR. KERR.—We used aerosol streptomycin here. One could not say that there was any very definite response to this treatment or that we observed anything except the spontaneous course of the disease. The child came in completely fatigued and whooped even harder for a day or so as her hydration and strength



improved, and thereafter she began to improve rapidly and her paroxysms lessened.

DR. SHAW.—I have seen worse cases of whooping cough but never more typical ones. I wish I had a sound recording of the whoop to save me the necessity of mimicking the paroxysm for succeeding classes of medical students.

#### COMMUNICABLE DISEASE DEPARTMENT

##### Four Cases of Bacteriemia

DR. E. B. SHAW.—We now consider a group of cases in which the etiology was established by blood culture. These cases of septicemia, although bacteriemia is probably a better word, are presented especially to point out the differences in blood stream infestation due to different organisms and particularly to point out the unique problem which is presented by meningococcemia.

DR. WILLIAM J. KERR (Resident Communicable Disease Service).—The first case will be presented by Dr. Randolph.

DR. RANDOLPH.—C. G. was admitted as a private patient of Dr. Roland T. Seitz. Three days before entry she complained of pain in her right thigh which became so severe as to cause her to be unable to walk. Her temperature gradually increased and on entry was 40.0° C. Examination at entry showed tenderness and swelling over the medial upper aspect of the right thigh. There was distinct limitation of motion of the right hip joint which was believed to be more on the basis of soft tissue infection rather than intrinsic inflammation of the joint. A small, crusted abrasion above the right external malleolus was evidently the result of a preceding abrasion and when the crust was removed there was present a minute draining sinus.

The remainder of the physical examination was negative although the child appeared quite ill. The white count was 6,650, polymorphonuclears 85 per cent, of which 54 were nonsegmented polymorphonuclear cells. Blood culture taken at entry later showed hemolytic *Staphylococcus aureus* which was demonstrated to be sensitive to penicillin.

Therapy was instituted on admission on the basis of a clinical diagnosis of staphylococcus bacteriemia and the child received throughout her stay full dosage of penicillin and sulfadiazine. There was prompt improvement in her general condition with a return of her temperature to normal after five days. She was placed in Buck's traction which relieved the muscle spasm. An x-ray of the hip taken several days after admission revealed a soft tissue swelling without demonstrable evidence of bone or hip joint involvement. She was dismissed ten days later entirely well and her subsequent course was uneventful.

DR. KERR.—This was considered to be a typical case of staphylococcus bacteriemia associated with a known point of entry. I should like Dr. Seitz, who was responsible for her care in the hospital, to discuss this case.

DR. R. P. SEITZ.—There is little to say about the onset symptoms except to say that these were initially very indefinite. The original abrasion, which was

occasioned by skating, was most innocuous in appearance. The presenting symptom was fever which was at first believed to be accounted for by influenza, which was current at the time. The rising temperature during the next forty-eight hours, the appearance of general toxemia, and the signs about the right hip gradually pointed to more serious possibilities and she was admitted to the hospital with a preliminary diagnosis of osteomyelitis. Therapy was promptly instituted and the confirmatory blood culture was returned five days later at a time when her clinical progress was entirely satisfactory.

This case, especially in its fortunate outcome, demonstrates the importance of initiating therapy on the basis of a clinical diagnosis and of obtaining blood cultures for the confirmation of diagnosis before therapy is commenced. This diagnostic procedure is especially important in the cases which may require prolonged therapy or in which the response to treatment is less dramatic. Blood culture and other materials for adequate bacteriological diagnosis must be secured before chemotherapy or antibiotic therapy is instituted.

DR. KERR.—The second case in this series is an example of beta hemolytic streptococcal bacteremia and it is significant that we had to go back to 1936 for a good example of this theretofore frequent syndrome. The patient, R. W., was admitted with otitis media and fever for a period of twelve days. His symptoms began with headache, fever, sore throat, and enlargement of the glands of the neck. Eight days before admission the left ear was painful and promptly spontaneously drained thick yellow pus. Six days before admission the right ear became similarly painful and developed a profuse purulent discharge. This child had had numerous preceding attacks of tonsillitis, otitis media, and cervical adenitis.

On entry the child was extremely ill, the temperature was 41.1° C., and there was a very marked pallor. The tonsils were huge, almost met in the midline, and were acutely inflamed. There was marked bilateral cervical adenopathy. Both ears showed a profuse discharge and there was tenderness over both mastoids. Apart from the general evidences of marked prostration, the remainder of the physical examination was noncontributory.

The blood count was: red blood cells, 2.6 million; white blood cells, 16,500; polymorphonuclears, 85 per cent. The urine showed occasional white blood cells and was otherwise negative. Cultures from the pharynx, from both ears, and from the blood showed beta hemolytic streptococcus.

Bilateral myringotomy was performed on the day of admission and on the fourth day thereafter a right mastoidectomy was performed. Because of the continued irregularly high fever and the profound degree of illness, the right mastoid area was re-explored on the sixteenth day of hospital stay; the right lateral sinus was exposed and was found not to be definitely thrombosed. With continued supportive therapy, including several transfusions, there was gradual improvement and he was eventually discharged well.

Dr. Gelston, who treated this patient in the hospital, will continue the discussion.

DR. C. F. GELSTON.—I am sorry to say that I have lost track of this boy since 1936, although he seemed entirely well when last seen. This case best

illustrates the difference in management of such problems only a few years ago and at the present time since the advent of various specific agents for therapy. Previously our only recourse was to surgery and such supportive therapy as transfusion, and these problems which were previously quite common have now become a rarity.

DR. SHAW.—I should like to point out that we had to go back to pre-sulfonamide days to discover, in our hospital, a good example of this form of beta hemolytic streptococcus bacteremia originating in the throat, involving the middle ears, spreading to the mastoid cells, and frequently provoking a thrombophlebitic process which often involved the lateral sinus with the production of an extremely septic temperature pattern and the picture of profound systemic infection. We used to see numerous examples of this type of infection every winter. The treatment of these infections was fascinating and sometimes fearful before the advent of modern therapeutic agents, and the end result was certainly unpredictable. We almost never see examples of this type of disease any more. Most of these forms of disseminated infection are simply cured before they begin by the use of sulfonamides, penicillin, and other antibiotics. Some of the nose and throat men still stubbornly insist that mastoiditis is not prevented by sulfonamides and penicillin but something very strange has happened to mastoiditis and mastoidectomies in the last few years.

The next two cases are presented as a contrast to these examples of staphylococcus and streptococcus bacteremia. Dr. Fischer.

DR. A. J. FISCHER.—This patient, L. K., was a 9-month-old white American child who was seen on the afternoon of Sept. 20, 1948, because of high fever of 40.0° C. When the child was examined by Dr. Lee Cohn he did not appear ill proportionately to the height of the fever and the physical findings were entirely negative. A tentative diagnosis of exanthem subitum was entertained. Overnight the child received symptomatic therapy and early the following morning the mother reported that the child's temperature was normal although she reported that a faint rash appeared on the hands and feet. By 10 A.M. the child's temperature had risen again to 40.0° C. and the rash had spread to become an extensive, confluent, hemorrhagic eruption. The child was promptly admitted to the hospital where he arrived in a state of complete collapse. The temperature was 41.0° C. and the pulse approximately 200, respirations 90. A confluent, hemorrhagic rash now involved most of the skin of all four extremities. The rash involved the face with occasional areas of clear skin around the bridge of the nose. Most of the trunk was spared although there were a few scattered areas of ecchymosis. The blood count showed intense hemoconcentration with a hemoglobin of 122 per cent; white blood cells, 5,100; polymorphonuclears, 36 per cent. Gram-negative diplococci were visible in many areas, especially within the polymorphonuclears, on an ordinary stained blood smear.

Intensive therapy was promptly instituted on admission: Penicillin and meningococcus antitoxin were given intravenously; sodium sulfadiazine was given subcutaneously; the child received an infusion of 300 c.c. of plasma; several injections of adrenal cortical extract were administered. Despite continued intensive therapy the child expired fifteen hours after admission.

Post-mortem examination showed markedly the extensive cutaneous ecchymosis and areas of ecchymosis were encountered in many of the viscera. The brain and meninges showed remarkably little evidence of damage. The lungs showed some areas of hemorrhage and some early pneumonia, especially in the left lower lobe. The liver and kidneys were quite normal in appearance. The adrenal glands showed only a minute area of hemorrhage in the cortex, while the medulla showed no grossly apparent hemorrhages.

DR. SHAW.—Kodachrome pictures of this patient were taken at the autopsy table under adverse lighting conditions. These pictures may not be satisfactory for reproduction but are very satisfactory for projection to illustrate the distribution and characteristics of the rash. You will note that the rash almost entirely involves the extremities and the face, the body being practically spared. There are a few small petechial spots but in general the rash is occasioned by diffuse ecchymosis which lacks the characteristics of embolic origin. The character of the eruption suggests a simple leakage of the blood through damaged vessel walls and this damage, I am satisfied, is due to an intense toxemia acting upon the intima of the vessels. The whole nature of this process is different from the other bacteriemias which we have presented. Meningococcus disease originates in an obscure infection in the upper air passages, this initial infection being sufficient to provide the production of vascular toxin which damages the vessels in such a way as to permit, on the one hand, ingress to the circulation of tremendous numbers of organisms and, on the other hand, provides the mechanism whereby blood cells and organisms escape from the circulation with the production of a typical hemorrhagic rash. In such a case as this the damage is irreversible by therapy directed against the multiplication of the meningococcus. This is often referred to as the Waterhouse-Friedrichsen syndrome, but this term adds little to the useful concept of the problem since it presupposes that adrenal hemorrhage is responsible for the severe shock and fulminant course. In this case and in more than one-half of our previous cases the adrenals did not show sufficient damage to constitute a primary factor in the symptomatology. It is a much more likely hypothesis that the damage throughout the body is dependent upon an extreme degree of intoxication which sometimes happens to damage the adrenals just as it does the skin and other organs. Furthermore, the intimal damage is quite distinct from the effects of bacterial or fibrin emboli encountered in other forms of bacteremia, especially that due to the streptococcus. Pathologic studies of Benda, Gruber, Herriek, and of Piek, together with numerous other investigators, satisfactorily establishes this conclusion.

I might inject a somewhat flippant note at this point which will nevertheless illustrate the extreme importance of the time element in treatment. Some years ago Dr. Henry Kempe inoculated a chick embryo with the spinal fluid from a patient with meningococcus disease. By the next morning the embryo was simply swimming in meningococci and the fetal movements were slowing down. Four hours after inoculation 50 units of penicillin were administered into the amniotic fluid and the egg was left in the incubator, where it hatched out into a normal chick.

(The picture was shown by projection.)

The chick seemed perfectly normal up to the time when it was presented to Dr. Danno, who took it to her ranch—where the cat ate it. This illustrates the rapid response of this organism to therapy and the potentiality for recovery if therapy is administered before irreversible damage has occurred.

DR. KERR.—A final case to be presented in this series illustrates a much more benign form of this same disease. This child, D. K., a 5½-year-old white girl, was seen by Dr. Thelander on the morning of admission with a petechial rash which had been noted only two hours previously. The child had been well until a few hours previously when she developed irritability, slight fever, and headache. Physical findings were limited to a petechial rash which diffusely involved the body, including the conjunctivae and the other mucous membranes. The throat was slightly injected and there was moderate neck stiffness. The white count was 21,800, polymorphonuclears 91.5 per cent, of which 45 per cent were nonfilamented. The spinal fluid showed 9 cells of which 4 were polymorphonuclear. The spinal fluid sugar and protein were normal. No bacterial growth was ever obtained from the spinal fluid. Blood culture was drawn before treatment was begun, and was positive for meningococci several days later. The patient was placed on procaine penicillin and in six hours the temperature dropped from 40.5° C. to normal levels, and she was dismissed after an uneventful course entirely well at the end of her quarantine period.

DR. SHAW.—This child responded to treatment as promptly as our chick embryo and was almost instantly well. Although the clinical diagnosis was promptly established by the purpuric eruption, the degree of severity was incomparably less than in the previous case and it is equally unlikely that adrenal damage was a significant part of the picture. It is of great importance to recognize promptly the significance of the purpuric eruption to the diagnosis. I recently saw a child at another hospital who had had a few days of mild illness and then suddenly became very ill with the development of a diffuse purpuric rash. The suspicion of meningococcus disease had been disarmed by the finding of a normal spinal fluid. Treatment with aureomycin had been instituted on a presumptive diagnosis of rickettsial disease. When I saw him two hours later he was greatly improved but the petechial eruption was so characteristic of meningococcemia that treatment was then instituted with sulfadiazine and by the next morning he was almost entirely well. There had been so much improvement after the single dose of aureomycin that I suspect that it actually cured this patient although I do not know of its being used in meningococcus disease. The final diagnosis was uncertain for five days when the blood culture, which had been drawn prior to any treatment, was returned positive for meningococcus, further reinforcing the belief that an extensive purpuric eruption of this sort nearly always means meningococcus disease.

DR. KERR.—In analyzing our autopsy material in this hospital during the last twenty years I find that among nine cases who died less than forty-eight hours after the onset of the disease adrenal hemorrhage was grossly present in three and was microscopically present in one. Dr. Fischer's case, which showed

extremely minute hemorrhage, was included among the three showing gross hemorrhage. Thus a total of four cases out of nine showed definite adrenal hemorrhage in fatal outcome. This percentage distribution of adrenal hemorrhage agrees fairly well with some of the literature. An excellent report by Ferguson and Chapman in the *American Journal of Pathology*, July 4, 1948, describes sixteen cases of fulminating meningococcus toxemia, among which there were nine which showed adrenal hemorrhage. These authors also subscribe to the view that the term Waterhouse-Friderichsen syndrome does little to clarify the picture and believe that toxemia and not adrenal damage is responsible for the fulminant advance of symptoms.

DR. SHAW.—We have presented two cases of localized pyogenic infection due to the staphylococcus and the streptococcus which resulted in sufficient blood stream infestation for the organism to be demonstrable by blood culture. In the days prior to sulfonamide and antibiotic therapy such examples of bacteremia were extremely common. In general, a positive throat culture in such instances is indicative of the degree of bacterial invasion. A local focus of infection immediately accessible to the blood stream readily results in bacteremia. Favorable conditions for this event particularly occur when local infection involves a heart valve, the blood vessel wall, or tissues immediately adjacent to a rich blood supply. A local thrombophlebitic process readily leads to bacteremia or pyemia through the dispersion of infected emboli. If neither the establishment of the original point of invasion nor the circulatory dispersion of infection is interfered with by antibiotic or chemotherapy, secondary foci of infection may be rapidly established and thus help to maintain blood stream infestation. Prior to modern efforts in therapy the control of these infections was dependent upon the resistance of the patient, the use of various supportive measures such as transfusion, and the final recourse to surgery in obliterating a local nidus of infection. At the present time the incidence of these bacteremias has been greatly reduced by the effective prevention not only of the original focus of infection but also of secondary disseminating foci equally accessible to the blood stream. We have attempted to illustrate that the problem of extreme infestation in meningococcus disease represents an entirely different mechanism of blood stream invasion in which rapid production of an intensely active vascular toxin is responsible for the ingress of organisms into the blood stream to an extent not comparable to most other pyogens, the same toxic agent being responsible for the easy egress of these organisms from the blood stream into vulnerable tissues. In meningococcus disease minimal therapy applied sufficiently early may effect a rapid cure, but if treatment is delayed, sometimes for even a short period of time, irreversible damage may be produced which is incapable of response to agents inimical to the infecting organism.

# Psychologic Aspects of Pediatrics

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## THE SUMMER CAMP

CORNELIA GOLDSMITH

NEW YORK, N. Y.

FOR children of today who live in cramped and congested large cities, in small apartments with remote and limited outdoor play space, and who attend crowded schools, a summer at a camp in the country is of increasing importance and popularity. New camps of all kinds are being established beyond the periphery of our big cities. The already existing ones are expanding their facilities to meet the growing demand. This rapid expansion of the summer camp movement applies both to the increasing numbers of children who go to summer camps and also to the broadening of the age span considered eligible for enrollment. More and more children, as well as younger and younger children, are leaving their homes during July and August each year to become "campers." It is not unusual to find camps enrolling 200, 300, or 400 children, or to find what are called "brother and sister camps" adjacent to one another under joint ownership and direction. A single day camp within the borders of New York City accommodates nearly 1,000 boys and girls from 3 to 16 years of age. Nor is it unusual to find increasing numbers of 2-, 3-, and 4-year-old children attending camps originally established for older children. These groups are commonly known as the "Midgets," the "Freshmen," or the "Tinies."

Since there are no established or generally accepted minimum standards or regulations governing camp operation except the sanitary requirements enforced by most State departments of health, anyone so inclined may set up a private camp regardless of his fitness or ability to do so. It is, therefore, important to help parents select a camp with utmost consideration as to whether or not it meets their own child's particular needs, whether or not the child is ready for such an experience, whether or not the camp, after careful investigation, is found to have a sound and constructive program, and whether it is operated under adequately qualified and responsible leadership. It can hardly be stressed too strongly that parents need help in choosing the proper camp for each and every individual youngster. Many young parents of today are refusing to send their children to camp because their own camp experience was too regimented, too ready-made, too overorganized. They had no chance to meditate or relax, to establish any real contact with country life, to use their own initiative, to step an inch off the beaten path, to move without being ordered or signalled by a whistle, a bell, or a gong. Everything they did had already been predigested by an adult and they invariably carried out someone else's plan to the exact letter. On the other hand, there is an increasing number of camps in which the campers have an opportunity to live worth-while country experiences, and where creative, competent leadership is provided.

Chief Division of Day Care and Foster Homes Bureau of Child Health, New York City Department of Health.

How, then, can parents know whether or not a particular camp is the kind they are looking for and whether it is suitable for their particular child?

#### CRITERIA FOR SELECTING A CAMP

1. Recognition that no two children think, feel, or behave exactly alike, even at the same age. It is necessary to be aware of and concerned with what is going on inside each child and it is necessary to treat each child as a human being and not a commodity that is being shipped away for the summer because he happens to have reached a certain age, or because it happens to suit someone's convenience, or because Daddy went off to camp at this same age. The child is the person most vitally concerned, and his attitude and his readiness should be primary factors in deciding when, whether, or where he goes to camp.

2. Proximity to home is a factor of particular importance to the younger child. Camp should be near enough so that a child under 10 or even under 12 may have several visits by his parents during the course of the camp season.

3. In terms of facilities, selection is relatively easy. Because most city homes of today have all modern conveniences, parents tend to require electricity, hot and cold showers with every bunk, et cetera. Innumerable camps do provide these conveniences. In fact, many compete with one another in building more and more luxurious and "swanky" facilities for the children, as though a camp were to be judged primarily by the number of its toilets and showers. When mere elegance in living quarters becomes a substitute for the kind of life that brings children into close contact with the out-of-doors, it is indeed a poor camp for any child. Facilities should be clean and sanitary, safe and dry, comfortable and preferably unostentatious. Children should have adequate space and adequate provision for eating, resting, sleeping, and for both active and quiet play, indoors and out. Simplicity, naturalness, usability should be the keynote rather than mere elegance, elaborateness, or impressiveness.

4. The program should accommodate itself to the interests and needs of the children themselves. City children are hungry for direct firsthand experiences with animals and plants, woods and fields, sand and earth, fire and water, fresh air and sunshine. They need, simultaneously, to exercise their hands and minds, their muscles and their creative powers of thought. Swimming, caring for pets, hiking, picnicking, making things, building things, sleeping out under the stars, walking in the rain, going barefoot, cooking over an open fire, gardening, working with tools, singing and story-telling around the campfire, fishing, frog-catching, building a dam, digging for worms, catching turtles and snakes, strolling through the woods, watching the stars or the fireflies at dusk, climbing, running, singing, dancing, dramatizing—these are important to any child. These are experiences of which most of our city children are too often deprived. For this deprivation camps can, to a certain extent, offer compensation. Programs rich in nature lore should be flexible, varied, interesting, and geared to the interests and abilities of each group of children.

5. Staff: The finest facilities in the world are of no benefit to children unless the director and the counsellors are also fine. However, their fineness must be far more than skin deep. Manners and appearance often impress par-



ents but these qualities alone are totally insufficient. Since the children are dependent upon the camp staff during their stay at camp they must be able to count on these adults fully and at all times for understanding, guidance, leadership, and protection. Each and every adult on the camp staff must be a person who has a genuine affection for children and who also likes country living and all the growing things and people about him. People who become camp directors or counsellors should have had some professional training and experience with children of the ages for whom they are responsible whether in the field of group work, camp counselling, education, or recreation. If it is important to have well-trained teachers for our schools, how much more important it is to have camp counsellors who live with our children twenty-four hours of the day and have full responsibility for their care and guidance, equally well trained and well selected! It is never sufficient to have people who say so glibly, "But I love children." The children must know that this love goes beyond words and gestures, and gives them real protection, security, and understanding. There should be a qualified physician as well as a trained nurse and a trained dietitian on the staff.

6. Equipment should be simple and sturdy. In the country children find great joy and satisfaction in working directly with raw materials and in handling essential tools. Raw materials such as clay, paint, wood, boxes, blocks, paper, sand, water, leaves, shells, etc., have infinite possibilities for their use. Tools such as hammers and saws, hoes, rakes, and trowels, shovels, wagons, wheelbarrows, buckets, looms, vise, clamps, brace and bit, etc., should be at hand to help the child to create freely in terms of his own interests and developing ideas. Equipment should be geared to the level of achievement of each age-level group, and to the skill and competence of that group. An easy, friendly framework of scheduled routines should be established which is planned and set up for the benefit of the children themselves and not actually for the mere convenience of the adults. Children do not need to be lined up, shouted at, whistled at, regimented, nor publicly humiliated at any time. Camps where this is the regular stock in trade should be shunned.

7. The intangibles, though hardest to measure, are truly the basic essentials in camp life. They exist in what we call the "atmosphere" of the camp, in the quality of the relationship between the children and the adults, as well as among the children themselves and the adults among themselves. Some conflicts and misunderstandings invariably occur in all group situations, just as they do in all family situations. What matters is how they are handled, how they are resolved, and what is the outcome. When conflicts are merely avoided and differences glibly covered over by adult tactics and not satisfactorily resolved, children never come to grips with themselves, with their own problems, or with each other. Real friendship, like all good human relationships, must have roots which must be nurtured. Even small things that go wrong must be handled in a real way, wisely and honestly, regardless of how trivial they may seem at the time. Otherwise molehills often grow to mountains and represent impenetrable barriers to growth and to good feeling. The camp staff should be sensitive to

group as well as individual problems and have skill and forthrightness in handling them.

8. The health of the children involves their physical, mental, and emotional health, if by health we mean each child's total well-being. From the physical aspect every camp, regardless of its size, should have isolation facilities with the nurse in charge. Approved first aid equipment should be available but kept out of reach of the children at all times. Every child should come to camp with the written report of a recent medical examination. Every member of the staff should have had a medical examination and chest x-ray just before coming to camp. Parents should be notified promptly whenever contagious disease develops in the camp. Good nourishing food, sleep, rest, and activity should all be appropriate, sufficient, and geared to the needs of the children themselves to prevent fatigue, strain, or overstimulation. Records of immunization and the contagious disease history should be available for every child.

9. *Additional benefits* may accrue to children in their camping experience if they have the opportunity to live in an intercultural group at camp. To enjoy living with people of different skin colors than their own, different national, social, and religious backgrounds, is an enriching experience which helps to prevent racial and religious prejudice from gaining a foothold. To know people naturally, without being made self-conscious about differences, gives children an added dimension in their living and a genuinely democratic approach to their thinking. Camps can provide such opportunities, free of rivalry, prejudice, artificial goals, or a distorted sense of human values.

#### DRAWBACKS TO CAMP LIFE

Now let us look briefly at the drawbacks and possible hazards to children in being sent to camps without the most careful preliminary study and selection:

1. *Overstimulation*.—Living in a group twenty-four hours a day is far more stimulating than living in a family. Children without proper guidance and controls may easily become overstimulated to the point of acute fatigue. Rather than building health, this undermines their physical and nervous structure and does them definite harm.

2. *Competition*.—Living in a group where competition is unduly stressed often creates such acute rivalry that it interferes with the development of normal friendly relations between children. Getting ahead, being best, winning the game, proving one's prowess supersede every other concern or interest and become the motivating drive, defeating all others. When the competitive element is stressed or featured, the children attain a false perspective, are determined to outdo and outdistance everyone else regardless of the effect on others, and lose the real benefits of their group experience. Such camps frequently set standards of achievement at such a high level that only the exceptional child can reach them. Consequently the majority of other children suffer frustration and a sense of defeat that leaves them with feelings of insecurity, inadequacy, inferiority, and hostility. Nevertheless, such camps continue to pride themselves on their high, unattainable standards. Many children are hurt far more than they are helped in such camps.

3. *Stereotyped Program.*—Where the program is fixed, set in advance in every detail, and every moment of each child's day is already accounted for on paper before he arrives at camp, it is obviously not geared to his needs or his interests. Such a program is mechanized and regimented and can have little real connection with, or meaning to, the children themselves. It is adult-imposed, inflexible, and essentially harmful. Children do not readily or willingly stay in such pre-ordained ruts and a considerable weight of adult control is needed to keep them there. This, too, is harmful. It develops increasing dependence rather than independence in children.

Every child's energy needs to be released naturally and constructively. He needs to express his own ideas, to explore and experiment with materials to use his inventive and creative powers, to develop initiative, judgment, skill, and confidence. To follow a fixed formula, set up in advance, makes him a mere mechanical automaton and robot. It hampers his development and stops his thinking. Children do not benefit by going to such a camp. Rather than being subjected to such harmful influence, a child should be kept at home.

4. When an insecure child or a too-young child is sent to camp before he or she is ready, great harm may be done. The child's first separation from home has dramatic, lasting, and profound meaning to him. If children are forced to go to camp, regardless of their willingness or readiness, the camp and the home are in league against them, pushing them irrevocably into a tragic and hopeless dilemma.

There are times during the growing up process when children need to spend a summer with their own parents more than they need anything else, whether or not the summer can be spent in the country. Considerate and aware parents will plan a summer around the needs of their children when this is the case. A family vacation may offer delights and reassurances that no camp can give, no matter how good.

A child gifted in any special area should not need a special camp for music or dramatics, for horseback riding or swimming, for arts and crafts or dancing. These activities should be an integral part of the program in every good camp, and every good camp should allow the special interests of children gifted in one field or another to thrive and to develop. Without being made to feel "special" these children can contribute richly to group plans and activities.

The handicapped child should also, whenever possible, be included in the regular group living of normal children. Unless the handicap is so acute as to require bed-care, or the entire attention of an adult, most average groups of normal children can absorb a not too severely handicapped child with benefit to all. To achieve this successfully it is essential that in such a group setup there is primary concern for the welfare of each individual camper, and different and conspicuous concern should not be shown exclusively for the welfare of the one child who may be handicapped.

To get sound, well-considered, professional advice regarding the selection of suitable camps to meet the differing needs of different children is difficult. Many camp counselling offices are set up by camp advertising publications, or by organized private camping groups themselves. Some are more reliable than

others. Objective, uncommercialized, professional advice in this field is greatly needed by parents. In the New York City area the Child Study Association of America has a full-time camp counsellor on its guidance staff, who gives consultant help to those parents who can come in for an interview. There is great need throughout the country for a sound, subsidized private camp advisory service.

Wherever possible, it is well to plan a year in advance as to the selection of a camp and to visit during the previous summer any camp under consideration, in order to observe it while it is in operation. This is perhaps the best way to be sure. Camp literature is only as reliable as the person who writes it. The pediatrician can help parents to analyze their motivation in sending a child to camp and the child's readiness to benefit by it, physically, mentally, and emotionally.

# Comments on Current Literature

## DEXTRAN AS A PLASMA SUBSTITUTE

IN A recent issue of *The Lancet* (Jan. 22, 1949) reports from Sweden<sup>1</sup> and Britain<sup>2</sup> on the use of dextran as a plasma substitute are presented. Since Bayliss<sup>3</sup> (1919) showed that a fluid which contained colloids having an osmotic pressure similar to that of plasma-proteins could be used as a substitute for blood, several substances, including starch, dextrin, gelatin, and gum arabic, have been used. Of these, gum arabic proved the most satisfactory. However, gum arabic was discarded because it was found to be stored in various organs and interfered with liver function. Other colloids, including pectin, polyvinyl alcohol, methyl cellulose, and polyvinyl pyrrolidone were used but with equivocal results. All of them showed storage phenomena to some extent.

In 1943, Grönwall and Ingelman<sup>4</sup> in Sweden suggested the use of dextran as a substitute for plasma. The material produced commercially under the name "Dextran Ph" is described by the Swedish firm, Pharmacia, as a 6 per cent solution of the polydispersoid glyucose-polymer, dextran, with 0.9 per cent sodium chloride added to it. This product is virus-free, does not lead to the formation of antigens, and contains almost no nitrogen. Its threadlike molecules are electrically neutral and chemically indifferent.

In Sweden, dextran has been given to 5,000 patients, 20,000 units having been infused. It was found to be nontoxic and produced no injury to tissues either locally or systemically. Thorsén<sup>1</sup> has shown by careful observations that "Dextran Ph" is useful as a substitute for blood and plasma in cases where an increase in blood volume or in colloidal osmotic pressure is desired.

Bull, Ricketts, Squire and their associates<sup>2</sup> verified these clinical results with the Swedish product and undertook more extensive studies with a British preparation of dextran. These authors define the theoretical requirements of a plasma substitute as follows:

### "Positive Qualities:

1. Its colloid solutes should be retained in the circulation until their place can be taken by the natural proteins. This implies that (a) the colloids should not pass readily into the tissue fluids nor be rapidly excreted by the kidney (a molecular size of at least 70,000 is, therefore, usually desirable); and (b) the colloid substance should not be rapidly metabolized or otherwise removed by the tissues.
2. The solution used for infusion should have an osmotic pressure and viscosity similar to those of plasma.
3. The composition from batch to batch should be constant, within narrow and definable limits.
4. The material should be stable during storage and preferably not require special conditions of temperature.

### "Negative Qualities:

5. It must not be toxic, either locally or generally.
6. It must not induce fever.
7. It must not induce sensitization.
8. It must not be stored for long periods in the tissues.
9. It must not act as a diuretic. Apart from the absence of specific diuretic properties, this implies that it should not contain large amounts of solutes of low molecular weight."

Dextran is considered by this group of workers as fulfilling most of these requirements. Their experimental observations indicated lack of toxicity, pyrogenicity, and antigenicity of the product and showed its value in the restoration of blood pressure in animals deprived by bleeding of approximately one-half their blood volume.

Immediately after infusion the erythrocyte-sedimentation rate was increased, its alteration varying with the plasma-dextran level. These findings were unassociated with any adverse clinical signs. Another interesting observation concerned the fact that a raised plasma-dextran level is always associated with a lowered plasma-protein level. When the plasma-dextran level falls, the plasma protein level rises again, and in several cases studied in detail, it was evident that the total of protein plus dextran tended to remain constant.

Preliminary clinical trials with British dextran were carried out on six patients with inoperable carcinoma. Aside from transient increase in jugular venous pressure in two patients, no untoward symptoms or signs were noted. The observers concluded that British dextran was bland, pyrogen-free, and well tolerated by the recipients. Subsequent to these preliminary trials, dextran was given to twenty-nine patients undergoing more or less severe surgical operations and to two patients with burns. While death occurred in one of the cases with burns, necropsy revealed no evidence that dextran contributed to the fatal outcome.

These studies indicated that dextran is well retained in the circulation, and that it can maintain the osmotic pressure until its place is taken by plasma proteins. The importance of the molecular weight of dextran is emphasized, since dextran of lower molecular weight escaped in the urine soon after infusion. The need for a uniform preparation with a defined range of molecular size is stressed by the authors, who point out that this must be worked out before reproducible clinical effects can be expected.

The evidence presented seems to favor the use of dextran as a plasma substitute. However, a word of caution is interjected since the ultimate fate of the preparation in the body is not certain. An ideal substitute for plasma should be metabolized completely or excreted. Until these facts are established, dextran cannot be recommended unreservedly. Apart from this uncertainty, dextran appears to be free from the disadvantages of other non-protein substitutes for plasma. The results reported in these recent studies are encouraging. The advantages of a readily available virus-free plasma or blood substitute are obvious. Should the claims of these workers be substantiated, it appears likely that hospital transfusion services may come to rely to a considerable extent on dextran for emergency cases.

RUSSELL J. BLATTNER

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## Book Reviews

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**Child Health Services and Pediatric Education**, The Commonwealth Fund, New York, N. Y., 1949, 296 pages. Price \$3.50.

In the winter and spring months of 1944 a number of conversations took place among Academy members culminating in the decision that postwar planning for initiating or extending child health programs on a national or local basis could be greatly facilitated by a survey of the existing health services and facilities for children throughout the United States. Such a proposal was placed before the Academy at its national meeting in St. Louis in November, 1944, and was unanimously adopted. President Gengenbach appointed a committee of nine which subsequently selected Dr. Warren Sisson of Boston as its Chairman. Dr. John Hubbard, also of Boston, and who was just terminating his period of war service, was chosen as the Executive Director. Both the U. S. Children's Bureau and the U. S. Public Health Service readily accepted the Academy's request to assist in the study.

Thus began one of the most unique undertakings ever attempted by an independent body of physicians. That it has been pushed through on an order of magnitude and to a degree of thoroughness far beyond the vision or expectation of those who initiated the idea is a testimonial to the abilities of the Academy organization, its state chairmen, and its Study Committee, with special laurels going to the Chairman, Director, and Executive Staff. Facts about the medical facilities and services for the care of children in the United States and about the training qualifications of those who render the care have been assembled which should be of inestimable aid in planning national and state child health programs for many years to come. That the Academy intends to make full use of the data collected and processed is shown by the appointment of a continuing committee, the Committee for the Improvement of Child Health.

The study has taken approximately three years to complete and about a million dollars. Publication of the findings in a two-volume set has been completed and is available for public inspection. Volume I is a general summary of child health services and pediatric education. Detailed tables and a description of techniques considered too voluminous to be included in the first volume are available in Volume II. In addition to these two volumes at the national level, each of the states is publishing its own report, from which it is hoped will come planning at the local and state level adapted to the needs peculiar to conditions in the individual state.

That portion of Volume I dealing with child health services consists of a foreword by Dr. Sisson and of seven chapters. It summarizes the information gathered from physicians and dentists and from hospitals and community health agencies. Chapter 1 outlines the plan and method of study and describes the basis of comparisons by state, region, and by county groups. Of especial interest is the method devised to compare health services available to rural and to urban children. It was recognized that many people living in rural areas are at the same time near enough to urban centers to permit easy access to the facilities of those centers. But in rural areas far removed from urban centers services received are, for the most part, restricted to those which can be obtained locally. Hence, five groups of counties were created—greater metropolitan, lesser metropolitan, adjacent, isolated semirural, and isolated rural. Greater

metropolitan counties are those in or around the twelve major cities of the United States. There are sixty-three of these. Lesser metropolitan counties are those which include all or portions of cities of 50,000 or more inhabitants. These number 177. Counties geographically contiguous to any of the metropolitan counties are classified as adjacent even though they in themselves may be predominantly rural. It is assumed that people in these adjacent counties readily cross county lines to avail themselves of the hospital facilities and specialists' services in the urban centers. There are 668 adjacent counties. An isolated semirural county is one in which there is one or more incorporated community of 2,500 or more inhabitants, and an isolated rural county is one in which there is no incorporated community of over 2,500 inhabitants. There are 1,116 of the former type of counties and 1,052 of the latter. Together they account for more than two-thirds of the total number of counties. Thirteen million of the total of 36,000,000 children under 15 years of age in the United States as of July 1, 1945, lived in the isolated semirural and isolated rural counties.

The next six chapters which give the data, well illustrated by charts, describe health services available to these two groups of children, the 13,000,000 in the isolated counties and the 23,000,000 in the metropolitan and adjacent counties. Comparisons are made on a state, region, and county group basis. For the purposes of this review, a few of the more striking comparisons are included in the following paragraphs.

The ratio of general hospital beds in relation to children in the metropolitan and adjacent counties is 15.4 beds per 1,000 children, while in the isolated counties the ratio is 8.4 beds per 1,000 children. It is not to be assumed, of course, that 15.4 beds per 1,000 children is the optimum number of beds which should be provided per 1,000 children throughout the nation, but it is clear that the number of hospital beds for rural children is deficient by nearly 50 per cent as compared to urban children.

Of interest is the distribution of physicians on a physician-child ratio according to county groups. In 1946 there were 116,795 physicians in private practice. This is one practicing physician for each 1,200 persons or 0.8 physician per 1,000 population. Related to child population the over-all rate becomes 3.2 physicians per 1,000 children. Analyzed according to county groups, there are 4.1 physicians for each 1,000 children in the metropolitan and adjacent counties as compared to 1.8 physicians per 1,000 children in the isolated counties. Thus, the 13,000,000 children residing in the isolated areas have less than one-half as many physicians per 1,000 of child population as do the 23,000,000 children who live in or close to urban areas. This discrepancy is probably not so important so far as specialists' services are concerned, for the child in need of a specialist's services can usually be transported to the specialist or vice versa, even though the distance be considerable. It is important, however, in the case of the general practitioners, for it seems reasonable that there should be at least an equal ratio of general practitioner service available for the rural child as for the urban child. In fact, it would be logical to argue that there should be more general practitioner service in the rural area since the full burden falls on the general practitioner's shoulders alone and the distance between patients is much greater. But instead of finding more general practitioners in rural areas we find fewer. There are 3.3 general practitioners for each 1,000 children in the greater metropolitan counties but only 1.2 in the isolated rural counties.

So far as distribution of dentists is concerned the situation is even worse. The national average is 1.8 dentists per 1,000 children, with a concentration of 3.4 dentists per 1,000 children in the greater metropolitan counties but only 0.6 in the isolated rural counties.



The deficiencies which exist in isolated counties in hospital beds, physicians, and dentists are shown in another way. One-third of the total population and, because rural families tend to be larger than urban families, 37 per cent of the children live in the two groups of isolated counties. Yet only 24 per cent of the total hospital beds, 21 per cent of physicians, and 19 per cent of the dentists are available locally to this portion of the population. To equalize the deficiencies in these three categories of health facilities would require at least a 50 per cent increase in hospital beds, doubling of the present count of 19,700 general practitioners, and tripling of the present number of 12,700 dentists in these isolated counties.

To compare the distribution of health services on a regional basis the country was divided into five regions—Northeast and Central, Southeast, Southwest, Mountain and Plains, and Pacific. The group of Southeastern states contains 6,000,000 children residing in isolated counties or nearly one-half of the total number of 13,000,000. Children in the isolated counties of the Pacific and Northeast-Central regions have two or three times as many hospital beds per child as in the states which make up the Southeastern region.

One might suppose that the deficiencies in rural areas in physicians' services would be compensated for in part by an increase in such community health services as well-child conferences, school health services, public health nursing service, and the like, but such is not the case. The Academy's study has revealed that these services are deficient in the isolated areas in about the same degree as the other health services already mentioned. In the year in which the study was being made, well-child conferences were held in only one-third of the counties in the United States. Two thousand thirteen counties, or two-thirds of the total, had no well-child conference. In 1,065 counties no public health nursing service for children was available and in 1,545 counties there was no organized program of medical service in public elementary schools. Community health services of these types are concentrated in urban areas where financial support is available.

One fact which the Academy's Study has sharply pointed up is the extent to which the children of America are dependent upon the general practitioners for their medical care. Seventy-five per cent of the total child visits in one day were made by general practitioners, 11 per cent by pediatricians and 14 per cent by other specialists. When broken down into county groupings it is seen that in greater metropolitan counties the general practitioner accounts for two-thirds of the child visits in private practice; in isolated counties, 98 per cent. A thousand children residing in predominantly urban states such as Illinois or Massachusetts on an average day receive over twice as much medical care as a thousand children living in such rural states as Mississippi or Alabama. If it can be assumed that children in urban areas are not getting too much medical care, then it follows that children living in rural areas are getting less than one-half the medical care they need. There is also the quality of medical care to be considered. Hospitals in cities have better laboratory, x-ray, and other diagnostic facilities than do rural hospitals. Children in and near cities have relatively twice as much hospital care, five times as much clinic care, and nearly five times as many visits to the pediatrician, while consultation services of other specialists are far more readily available. All this adds up to the conclusion that the city child has greater opportunity for health than the country child. In fact, the infant mortality rate for the five years of 1941 to 1945 was thirty-eight for the metropolitan area and forty-seven for the isolated counties.

Clearly, the study as summarized in the report has demonstrated beyond question the maladjustment of health services for children in the United States. This should not be interpreted as taking anything away from the fine

record of progress which has been made by this country in the care of its children. *It is a fine record and one of which every citizen in America may be justly proud.* But the point is, can a still better job be done? The answer to this is a definite yes, and the study has certainly achieved its primary objective of pointing out some of the things that need to be done in order that the health of all our children may be improved still further. Perhaps a closing comment or two on this point may be permitted.

There are some 3,500 pediatricians in practice in the entire United States. Three-fourths of these live in cities of 50,000 or more population. There would seem to be no prospect whatever in the foreseeable future that the number of pediatricians will be increased sufficiently to provide pediatric care even for the children in the metropolitan areas alone, to say nothing of the rural areas although the need for more pediatricians is great. Any approach to improving the health services and facilities for all children must, therefore, be centered around the general practitioners. First of all, there needs to be more of them, and more of them in rural areas. They prefer to live in the urban areas where hospital, laboratory, x-ray, and specialist services are more readily available, and where their families can have the advantages that go with urban living.

Unquestionably, the construction of hospitals and health centers in rural areas as provided for under the Hill-Burton Act will do much to attract more general practitioners to rural areas, but the job is not one of easy solution. For unless laboratory, x-ray, and other technical personnel and facilities are provided to staff these institutions, the rural physician will still lack important tools needed for the practice of good medicine. A major share of the responsibility for the securing of adequate community health services, including physicians, nurses, and public health units, would seem to rest with the communities themselves. Initiative in this direction, if pursued with sufficient zeal, might be successful in many instances. A problem of equal, if not greater, significance so far as children are concerned to that of increasing the number of general practitioners in rural areas is the problem of increasing the pediatric training of the general practitioner. Since 75 per cent of the children of the nation are dependent upon the general practitioners for their pediatric care, it is clear that any improvement in the health of children on a nationwide scale must come about through better pediatrically trained general practitioners. Approximately one-third of the visits made by the general practitioner on an average day are made to children under 15 years of age, and yet nowhere near one-third of his undergraduate or postgraduate training is spent in pediatrics. But this leads directly to that portion of the report which deals with Pediatric Education. There needs to be added here only a word of congratulation on the excellence of the report and an expression of hope that it will find the field of usefulness which it richly deserves.

L. F. HILL.

#### PEDIATRIC EDUCATION

In the final analysis the medical care which a child receives is dependent on the knowledge of the physician responsible for his care, and this, in large measure, depends on the physician's training. It was for this reason that a study of pediatric education became an integral and necessary part of the study of child health services. A subcommittee of pediatric teachers, with Dr. James L. Wilson as chairman, was formed to outline the study. Dr. John McK. Mitchell, the present Dean of the University of Pennsylvania Medical School, became Director of the study. In the school year 1946-1947 and the first semester of 1947-1948, he made personal visits to each of the seventy approved medical schools in the United States. A separate study of pediatrics in the Canadian medical schools, which follows a similar outline and in which Dr. Mitchell has

cooperated, is being made. Regional meetings of the heads of the pediatric departments were held prior to the visits, and thus each school was familiar with the data sought for the study.

The information developed by the study will, beyond question, have a tremendous influence on pediatric education as a whole, particularly in light of the findings of pediatric care in Part I of the study. Let us say at the start of the review of this Part that in the breadth and scope of the report, and in the vast amount of data that have been obtained and analyzed, the Director, Staff, and Committee in charge have done a magnificent job and deserve the thanks of not only medical educators, but of all those who in one way or another are interested in the better health and medical care of children.

The report on education, pages 141 to 250 of the volume, is divided into two parts, A—Undergraduate Education, which is subdivided into ten chapters, and B—Graduate Education, with five chapters. To this is added a summary, bibliography, and appendix tables. Thirteen graphs or charts are used to illustrate the material.

Chapter 9 discusses the seventy medical schools, their location and affiliations. Chapter 10 is concerned with student enrollment and admission requirements. It is estimated that in 1948, 21,878 individuals applied for the approximately 6,000 places available in the medical schools. The report calls attention to the increase in medical students admitted in 1946-1947 being 7 per cent over the admissions in the same schools in 1939-1940. The report states that under present conditions a further increase in the number of students in existing schools would jeopardize the quality of teaching in most schools, as they have expanded to the limit compatible with adequate standards of education. All but three schools in 1947 admitted women, and forty-six had a policy of accepting Negroes if properly qualified. With these two excellent summaries of medical school conditions as a background, the report turns directly to its immediate problems of pediatric education.

In Chapter 11 on Departmental Organization we learn with astonishment that in 1947 in four of the seventy medical schools, pediatrics was still a sub-department of internal medicine—this despite the position of pediatrics in medical practice and the recommendation of the Council on Medical Education in 1935 that pediatrics should be recognized as a major clinical department. One can seriously question whether these schools should be continued on the list of approved schools.

In Chapter 12 on Budgets we reach one of the most important phases of the study. Much of this has already appeared in print in one form or another and is the basis of the movement for Federal support of pediatric education which has been the subject of controversy. The report recognizes the many difficulties in obtaining figures of departmental expenditure for comparative purposes, but even with the inaccuracies that are acknowledged, the over-all picture to the reviewer is a clear-cut presentation which may be accepted as valid. There are tremendous differences in the budgets of the pediatric departments. Thus nine schools have an income of over \$100,000 per year and eleven less than \$5,000. The average is approximately \$44,000, but the median is \$25,000. While the large budgets of some schools (the highest is between \$250,000 and \$300,000) are not a necessity for good pediatric teaching, budgets under \$10,000 to \$15,000 are beyond question totally inadequate. The variation is more striking and the comparison more to the point when consideration is made on the basis of the number of medical students in the school. In five schools it is less than \$10 per student per year and in four, over \$400. Twenty-five had less than \$50 per student, twenty-five between \$50 and \$200, and twenty over \$200. In forty-three schools the amount was less than \$100 and in twenty-seven over \$100.

In the various medical schools there are 460 pediatric staff members who give at least one-quarter of their time to teaching. About one-fifth of these derive their entire support from private practice. One-half serve on a part-time basis and receive a small, often only a token, salary which does not represent an appreciable contribution to their income. To quote directly from the report, "Great honor is due to the group of loyal and conscientious pediatricians who give so freely of their time and energy without recompense in order that medical teaching may go on. At a reasonable estimate there would be no department of pediatrics in twenty-eight schools if it were not for these physicians and the ones who receive a purely inconsequential sum." Not only is there a crisis in medical education which has been the subject of so much discussion, but financial support is obviously the crux of the situation. On careful study of the report it is easy to see why the Committee on Improvement of Child Health urged Federal aid for pediatric education. It is a method of financing medical education which is steadily gaining the support of medical educators.

The organization of the staff of pediatric departments, as discussed in Chapter 13, shows that in seven schools the pediatric staff is essentially on a full-time basis, in thirty-nine a combination of full- and part-time members, and in twenty-four the staff is entirely part-time. Of the thirty-nine schools with a combination staff, twenty-one were "essentially full-time" and thirteen "essentially part-time." In five schools no differentiation could be made. Thus the departments in twenty-eight schools may be considered on the "full-time" basis and in thirty-seven on "part-time." In thirty-one schools the head of the department is on full-time and on an average gives 60 per cent of his time to administration. The study then goes into such details as teaching hours and other activities of the staff members.

The teaching hours allotted to pediatrics in the medical school curriculum show a decided increase when compared with the hours twenty years ago. Thus in Chapter 14 we find that the average school in 1946-1947 had 286 scheduled "catalogue hours" for pediatrics. However, there were, in addition, on an average, twenty-eight "overtime hours" spent by each student. This is about 11 per cent of the instruction in the junior and senior years. This figure is of interest in the finding of Part I, in which it is disclosed that almost one-third of the average day's work of the general practitioner is with children. More and more emphasis is placed on the clinical clerkship as a method of instruction, with didactic teaching, particularly in the form of lectures, playing a smaller role in instruction. In five schools no formal lectures are given but in one it still constitutes over one-half of the instruction. The importance of outpatient teaching is stressed, together with its place in the curriculum. The final discussion is on the place of subspecialty teaching as allergy, child psychiatry, etc. The number of hours that should be allotted to pediatrics depends, of course, on the facilities available for teaching. It would be a waste of the student's time to increase hours without suitable facilities and material. This wide variation is shown by some schools allotting over 400 hours to pediatrics, and nine still under 200. Two hundred hours was the minimum suggested nearly twenty years ago as necessary for pediatrics. However, by and large, the report shows that the importance of pediatrics has steadily gained recognition in the crowded medical curriculum.

The next two chapters discuss the teaching of certain special phases of pediatrics as the newborn and premature infant, and the integration of social and environmental factors. Direct student contact with the newborn infant is a difficult technical problem. In less than one-half of the schools is opportunity provided for the student to perform physical examinations on newborn infants. In fifty-nine of the seventy schools the training of the student in the care of the newborn infant is the responsibility of the pediatric department. The opportunity for observation of the handicapped child is extremely spotty.

Chapter 17 takes up the all-important question of facilities. Hours assigned to any clinical subject are largely wasted if sufficient clinical material is not available. The average medical school has ninety-one beds directly under the control of the department, but one-half have less than 115. Many schools have, in addition, "supervisory beds" where teaching is done by members of the staff. Twenty-two schools have less than one bed per senior student while forty-eight have one or more. This does not include bassinets. Twenty schools have less than fifteen bassinets for teaching the care of the newborn infant. Facilities for teaching the communicable diseases are grossly inadequate in thirteen schools and in only thirty-four can the facilities be considered as satisfactory. Outpatient facilities which are so important for undergraduate teaching show wide variation. In thirty-two schools there are 100 or more visits annually per senior student, but two schools have less than twenty-five annually. The desirable ratio of one new and two to three old visits per student at each outpatient session is not found in many schools.

One of the most interesting discussions is the final chapter on undergraduate education which describes the rating of the pediatric instruction in the various schools on an objective basis. A rating sheet was devised by the staff and a committee of department heads which contained fifteen specific items with a numerical value assigned to each. The total value of the points amounted to 100 with a maximum possible score assigned as follows: staff 40, clinical facilities 22, content of pediatric course 27, budget 11. A second subjective rating was made on the impressions of each department based on certain intangibles as the spirit, reaction of student body to course, interest in research, etc. Such an over-all correlation was established with the purely objective rating that the subjective scoring was abandoned.

On the basis of the objective rating, twenty schools were placed in a high group, all of which had scores of 70 or more, thirty were placed in a middle group, and twenty schools with a score of 40 or less were placed in a low group. The discussion then goes on with a detailed comparison of the various items of rating in the high and low groups of schools. The high group had four times the teaching hours of the low group expressed in terms of the ratio of teaching hours to student enrollment, and far more in- and outpatient clinical facilities per student. The most striking difference is found in the budgets. The department budget for the high group averaged \$90,000 and for the low \$7,400. The high averaged \$300 per student and the low \$25. Five per cent of the whole school budget, which amounted on an average to \$2,700 per student, was allotted to pediatric teaching in the high group, as contrasted with 1.1 per cent of the budget of \$1,200 per student in the low scoring group of schools.

To the reviewer the conclusion is inescapable that if there is to be better pediatric teaching and training of American doctors, more money must be found for medical education, particularly for the schools in the low scoring group. This is the underlying cause of the marked differences in the extent and character of the teaching of pediatrics in our medical schools.

In Chapter 19 the report turns to the survey of graduate education in pediatrics. While the medical schools have assumed no direct responsibility for the program, a large part of the graduate instruction is in the teaching hospitals where it is carried out by members of the clinical faculty. No attempt was made to study the extent of pediatric training in 764 hospitals approved for general intern training. There are 180 hospitals approved by the Council on Medical Education and Hospitals of the A. M. A. for residencies in pediatrics, and 158 of these were visited by members of the study staff. Twelve of the 180 had not been approved at the time of the study. Ninety of the 158 hospitals were teaching hospitals definitely integrated with the medical schools, and sixty-eight are not used for undergraduate pediatric teaching. The first year of hospital

training following immediately after graduation is generally classified as "internship." There are 187 such positions of which all but five are in the teaching hospitals. A full-time house staff position the second year after completion of an internship is classified as an "assistant residency." There are 450 assistant residencies approved, of which 357 are in the teaching hospitals and ninety-three in the nonteaching group. The positions the second year of pediatric training after internship are classified as "residents." There are 206 such places available of which 129 are in the teaching hospitals and seventy-seven in the nonteaching. Thus there are a total of 843 pediatric hospital services of a term of one year available, of which 80 per cent are in the teaching hospitals. As the American Board of Pediatrics requires two years of training at the residency level, the 656 assistant resident and resident positions provide for only one-half that number of individuals. Were all these approved residencies wholly satisfactory, it would seem to the reviewer that the opportunities for specialist training were adequate in number. Unfortunately, as is brought out in subsequent chapters, some residencies offer a far better experience and training than others. This coincides with the examination experience of the American Board of Pediatrics over the past fifteen years.

In the 158 hospitals there are, in addition, 253 positions of rotating internship for a shorter period, usually of from one month to six weeks, which provide some graduate pediatric teaching for approximately 2,000 recent graduates. But taken as a whole only 2,300 interns receive pediatric training in the hospitals approved for pediatric residencies, and 3,400 are without such experience. Certainly this finding raises an issue that needs considerable study and thought on the part of those concerned with pediatric education. To the reviewer it raises the question as to whether or not we have gone too far in the training of specialists in our children's hospitals at the expense of the education of the general practitioner who looks after the health of 75 per cent of the children.

Chapters 20, 21, and 22 are detailed discussions of the in- and outpatient training of the residents. Some hospitals have too few admissions per resident to give a broad experience and a few too many for proper study of the case. In some the newborn service is inadequate and in others the contagious. In seventy-seven of the hospitals there is little or no "well-child service," although in the survey of practice it was found that 54 per cent of all visits made by pediatricians in private practice are concerned with this phase of medical care.

Chapter 23 discusses the extent of ward rounds and conferences in the hospitals which form the basis of the "teaching" in graduate education and are of particular interest to the educator.

To the reviewer the survey and report on pediatric education leave certain impressions as a whole. First, the tremendous improvement in pediatric teaching which has steadily been taking place in recent years. As compared with the situation twenty years ago when the White House Conference study was made, the progress is amazing. It is obvious that there are many fine pediatric clinics in the United States today, when thirty years ago they could have been counted on the fingers of one hand. Second, where weaknesses exist the fault is chiefly one of budget limitations. Third, the thoroughness of the report and analysis of the data obtained on the survey. This, together with the fairness of interpretation and the broadness of viewpoint of those responsible, makes it a study of monumental value to those concerned with the care of children.

VEEDER.

## News and Notes

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Dr. Eugene Rush, chief of the pediatric service at the Mount Sinai Hospital in Philadelphia, died February 19, 1949.

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The Second Pan American Pediatrics Congress will be held at the Hospital Infantil, Mexico City, Mexico, Nov. 2 to 5, 1949. The following plenary sessions are scheduled:

- Nov. 2. Acute Diarrheas in Infancy  
Hemolytic Syndromes of the Newborn
  - Nov. 3. Congenital Malformations of the Heart  
B.C.G. Vaccination in America
  - Nov. 4. Pediatric Surgery  
Virus Diseases in Pediatrics
  - Nov. 5. Child Neuropsychiatry  
Pediatrics in the Field of Social Security
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The following were certified by the American Board of Pediatrics at the examination in St. Louis, Feb. 18, 19, 20, 1949.

- Dr. Eugene W. Austin, 216 S. E. Riverside Drive, Evansville, Ind.
- Dr. Curtis A. Beerman, 300 Lincoln St., Johnstown, Pa.
- Dr. Milton Carl Bessire, 1052 North 5th St., Abilene, Texas.
- Dr. Richard Charles Brown, 113 E. Williams St., Owosso, Mich.
- Dr. Joseph A. Browning, 184 Washington N. E., Warren, Ohio.
- Dr. Cho Duke Choy, 920 East 59th Street, Chicago 37, Ill.
- Dr. Harold S. Cole, 19 Donaldson Avenue, Rutherford, N. J.
- Dr. Clyde Douglas Conrad, Medical College of South Carolina, Charleston, S. C.
- Dr. James T. Cowart, Lafayette Office Building, Tampa, Fla.
- Dr. Harry M. Estes, 225 Bennie Dillon Bldg., Nashville 3, Tenn.
- Dr. Matthew Feldman, 120 Bogert Road, River Edge, N. J.
- Dr. Paul M. S. Fischer, Pediatric Dept., Univ. Hospital, Ann Arbor, Mich.
- Dr. Samuel W. Gollub, 4500 Olive St., St. Louis 8, Mo.
- Dr. William Burton Greenberg, 315 60th St., West New York, N. J.
- Dr. Caldwell K. Hamilton, Missouri Theater Bldg., 634 N. Grand Blvd., St. Louis 3, Mo.
- Dr. Olga Romanov Hoffman, 57 Park Terrace Gardens E, New York City 34, N. Y.
- Dr. S. Sprigg Jacob, 401 W. Grand River, East Lansing, Mich.
- Dr. Max Kaplan, 1575 Gilpin Street, Denver 6, Colo.
- Dr. Robert Emmett Keeley, 2376 E. 71st St., Chicago, Ill.
- Dr. Howard L. Lange, First National Bank Bldg., Belleville, Ill.
- Dr. Sidney S. Marder, 116-50 227th St., St. Albans 11, N. Y.
- Dr. Beryl M. McDonald, 1102 Broadway, Rockford, Ill.
- Dr. Luther L. McDougal, Jr., 705 West Main St., Tupelo, Miss.
- Dr. Conn Lewis Milburn, Jr., School of Medicine, Western Reserve Univ., Cleveland, Ohio.
- Dr. James Urban Morrison, Jr., 1430 Tulane Avenue, New Orleans, La.
- Dr. Herbert F. Philipsborn, Jr., 706 Glencoe Road, Glencoe, Ill.
- Dr. Elliott Podoll, 2114 Weber Avenue, Louisville, Ky.
- Dr. Ivan J. Roggen, 716 Malzaan St., Saginaw, Mich.
- Dr. Wendell Linwood Severy, 4614 Sunset Blvd., Los Angeles 27, Calif.

Dr. Vincent Arthur Spinelli, 27 Ludlow St., Yonkers, N. Y.  
Dr. LeRoy J. Stephens, 3284 Ivanhoe St., St. Louis 9, Mo.  
Dr. Edward Louis Strem, 711 Lowry Medical Arts Building, St. Paul 2, Minn.  
Dr. John D. Stull, 106 North Silver St., Olney, Ill.  
Dr. James Mack Sutton, Jr., 412 Third St., Albany, Ga.  
Dr. Edward H. Townsend, Jr., 26 South Goodman St., Rochester, N. Y.  
Dr. Robert Warner, 333 Linwood Avenue, Buffalo, N. Y.  
Dr. Erle Ewing Wilkinson, 415 Chesterfield Avenue, Nashville, Tenn.  
Dr. James N. Yamazaki, Children's Hospital, Cincinnati 29, Ohio.

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The staff of the Children's Hospital in Denver, Colo., will hold a three-day summer clinic session June 30, 31, and July 1. There will be three full days of demonstrations and panel discussions. In addition to the regular pediatric and surgical staff, Dr. Mitchell Rubin of Buffalo, Dr. Wolf Zuelzer of Detroit, and Dr. Willis Potts of Chicago, will be guest speakers. Full information may be obtained from the hospital.

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Dr. Louis K. Diamond of Boston, who has been acting as part-time technical director of the Red Cross Blood Program, has been given a temporary leave of absence from the Harvard Medical School and Children's Medical Center at Boston to assume the full-time position of medical director of the Red Cross program. Between January, 1948, and mid-February, 1949, the Red Cross had opened nineteen regional centers and one statewide mobile unit. By June, 1949, a total of thirty regional centers and programs are expected to be in operation.

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The birth rate for 1948 was only 4 per cent under the rate for 1947, making it the second largest year in the history of the country. The 1947 rate was increased 50 per cent or more over 1940 in fifteen states, and between 40 and 50 per cent in fifteen others. Again history repeats itself with a high birth rate accompanying and following a war.

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The Second Commonwealth and Empire Health and Tuberculosis Conference will be held in London, July 5 to 8, 1949.

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Memorial Hospital Center for Cancer and Allied Diseases, New York, N. Y., has established a residency in pediatrics. The period of service is for a minimum of six months and its purpose is to train the pediatrician in the diagnosis and management of neoplastic diseases in childhood. The resident will also participate in the research program in progress at the Sloan-Kettering Institute. Three months' credit toward Pediatric Residency training requirements has been approved by the American Board of Pediatrics. For further particulars applicants may communicate with the Director, Pediatric Service, Memorial Hospital Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.



# Editor's Column

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## THE SURVEY OF PEDIATRIC SERVICE AND EDUCATION

AT A dinner at the Roosevelt Hotel in New York on April 2, the report of the "Study of Child Health Services and Pediatric Education in the United States" was made public. Because of its importance, it is extensively reviewed on page 518 of this issue. Since the study was undertaken and sponsored by the Academy of Pediatrics at its meeting in the fall of 1944, not only over a million dollars, but thousands of hours of the time of busy doctors have gone into the study. The survey staff worked unceasingly for over two years on compiling and analyzing data. Nothing like it has ever been done before and the pediatricians of America may look with pride on their attempt to evaluate the medical care which the children of the United States receive. Sound planning for the future depends on our knowledge of what is and what is not being done. This was the thought that led to the study. But the study is not an end in itself, it is only the current balance sheet of credits and debits. Now the real task comes of implementing the findings and recommendations into terms of definite action. The two most important conclusions on the basis of the findings of the survey are first, the need of better training in pediatrics for the general practitioner, and second, making it possible for children in isolated areas to receive medical and health care comparable to that in the larger metropolitan areas.

Our hats go off to all who are responsible for and aided in the work of the study and the report.

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## CANCER IN CHILDREN

IT IS rather startling to find that cancer, including leucemia, is now the second leading cause of deaths from disease in children between the ages of 1 and 14 years, and is the leading cause of deaths from disease in the 5- to 9-year age group.\* In 1930 it was not even in the first ten causes. This change is due, of course, to the lowered mortality from the infectious diseases due to preventive measures and to the introduction of the sulfa drugs and antibiotics. Over 2,000 children die from cancer in the United States each year. Leucemia is the most common type of cancer, accounting for one-half of the cancer deaths in the 1- to 4-year age group, and two-fifths in the 5- to 9-year group. In the younger children, bladder and kidney cancer ranks second, and in older children brain tumor. Some of the increase in the number of reported deaths from cancer in recent years in all probability is accounted for by more accurate diagnosis. That all cancer in childhood is not hopeless was shown by Dargeon,† who reported patients living five to ten years after the beginning of treatment. As with adults, the earlier the diagnosis and starting of treatment, the more favorable the chances of survival.

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\*Reported in the Statistical Bulletin of the Metropolitan Life Insurance Company for January, 1949.

†Dargeon, H. W.: Cancer in Children, J. A. M. A. 136: 459, 1948.

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## Original Communications

### VITAMIN B<sub>12</sub> THERAPY IN MEGALOBLASTIC ANEMIA OF INFANCY

A. Z. MCPHERSON, M.D., U. JONSSON, M.D., AND R. W. RUNDLES, Ph.D., M.D.  
DURHAM, N. C.

A SEVERE anemia occurring in infants under the age of 18 months with megaloblastic blood formation in the bone marrow has been recognized with increasing frequency in recent years.<sup>1-6, 12, 13</sup> Infection and feeding difficulties predisposing to dietary inadequacy are common antecedents. The anemia responds specifically to liver extract or to pteroylglutamic acid therapy.<sup>2, 3, 5, 9, 12, 13</sup>

The clinical findings in different cases are highly variable. The anemia may be normochromic and normocytic, or macrocytic. The red blood cells usually vary greatly in size and in shape and show evidence of disturbed maturation. There is a tendency toward leucopenia, neutropenia, and thrombopenia. Some infants are jaundiced. Free hydrochloric acid may or may not be present in the gastric contents. Examination of the bone marrow is usually necessary to establish the diagnosis.<sup>12</sup> Injections of liver extract or pteroylglutamic acid given orally or parenterally are effective therapeutically, although the rate of response is variable. A reticulocytosis is induced which usually reaches a maximum in from six to eight days and a normal type of erythropoiesis is restored in the bone marrow.<sup>12</sup> After the anemia is once corrected, specific therapy generally does not need to be continued.

Rickes and co-workers<sup>7</sup> have recently isolated from liver a new crystalline compound containing cobalt which in microgram quantities induces hematologic and clinical responses in patients with pernicious anemia.<sup>8, 10, 11</sup> Preliminary estimates indicate that one microgram of this substance, designated vitamin B<sub>12</sub>, is equivalent to 1 U.S.P. unit of liver extract. We have treated two infants with megaloblastic anemia with vitamin B<sub>12</sub>. Their case histories follow.

#### CASE REPORTS

CASE 1, J. B. J., C-43272.—This 11-month-old Negro girl was first brought to the Pediatric Clinic of Duke Hospital on Sept. 7, 1948, with the chief complaints of weakness, constipation, and colic.

At birth the infant appeared to be healthy. After the age of one month she cried a great deal, nursed poorly, and appeared to have considerable colicky

From the Departments of Pediatrics and Medicine, Duke University School of Medicine, and the Hematology Laboratory, Duke Hospital.

Vitamin B<sub>12</sub> was supplied through the courtesy of Dr. Augustus Gibson, Merck & Co., Inc. This work was supported by a grant from the Anna H. Hanes Fund.

TABLE I. HEMATOLOGIC FINDINGS IN CASE I, J. B. J., C-43272

DATE	Hb. (GM. PER 100 C.C.)	RBC (MILLIONS PER C.C.)	WBC	HEMATOCRIT	MEAN CORPUSCULAR VOLUME (CUM.)	RETICULO-CYTE (PER CENT)	PLATELETS	DIFFERENTIAL WBC AND THERAPY
9/15	3.2	1.1	20,000	10	92	7.4	27,000	Segmented polymorphonuclears 31, metamyelocytes 1, myelocytes 3, myeloblasts 1, lymphocytes 48, monocytes 2, eosinophiles 12, nucleated RBC 12/100 WBC.
9/16	<i>Tibial Marrow:</i> Segmented polymorphonuclear 1.75, stabs 9.5, metamyelocytes 2.5, myelocytes 6.75, myeloblasts 0.25, lymphocytes 3, eosinophiles 8, plasma cells 0.25, acidophilic megakaryoblasts 23, basophilic megakaryoblasts 35.5, promegakaryoblasts 9.5. Leucocyte: nucleated red cell ratio = 1:2.2							
9/17	2.9	0.92	26,000	8.5	92	5.8	34,000	Vitamin B <sub>12</sub> 0.002 mg.
9/18						8.7		
9/19						10.5		
9/20	3.5	1.1				26.8		
9/21	4.5	1.3				46.1		
9/22	5.4	1.5				53.9		
9/23	6.5	2.0				49.5		
9/24	6.6	2.2	19,000	24	108	69.1		
9/25						24.6		
	<i>Tibial Marrow:</i> Segmented polymorphonuclears 11, stabs 23, metamyelocytes 5.5, myelocytes 5, myeloblasts 0.5, lymphocytes 0.5, eosinophiles 6, plasma cells 0.5, acidophilic megakaryoblasts 25, basophilic megakaryoblasts 20, promegakaryoblasts 3. Leucocyte: nucleated red cell ratio = 1:1.1							
9/26						12.3		
9/27						10.9		
9/28	7.8	2.6	17,150	28	107	12.0		
9/29						12.2		
9/30						13.7		
	<i>Tibial Marrow:</i> Segmented polymorphonuclears 13, stabs 21, metamyelocytes 4, myelocytes 5, myeloblasts 0.5, lymphocytes 2.5, eosinophiles 5.5, acidophilic normoblasts 31.5, basophilic normoblasts 14, pronormoblasts 3. Leucocyte: nucleated red cell ratio = 1:1.1							
10/1	7.8	2.8	13,350	30	104	13.5	Abundant	Segmented polymorphonuclears 73, lymphocytes 16, monocytes 3, eosinophiles 8, nucleated RBC 2/100 WBC.
10/22	10.0	3.2	15,050	30.5	94	1.3	Abundant	Segmented polymorphonuclears 61, lymphocytes 27, monocytes 6, eosinophiles 6.
12/8	12.2	4.0	11,650	37.0	93	0.8		

abdominal pain. Bowel movements became infrequent. Her abdominal pain seemed to be worse when she was given cereal or vegetables. Consequently her diet was restricted to breast milk without the addition of solid foods, orange juice, or cod liver oil. During the first six months her growth and development appeared to be normal. Subsequent development was slow, and she made no attempt to crawl or walk. Two weeks before being brought to the clinic she became particularly irritable, fretful, and slightly febrile. The family physician prescribed powders and injected penicillin intramuscularly, but there was no symptomatic benefit.

Four older siblings and the parents were healthy.

Physical examination in the out-patient clinic showed a moderately well-developed and well-nourished Negro infant who was very fretful and irritable. The rectal temperature was 37.5° C. and the weight 13½ pounds. The mucous membranes and nail beds were very pale. There was no jaundice. The heart was enlarged. The liver was palpable 2 cm. below the right costal margin. Serologic tests for syphilis and a test for red cell sickling were negative. The hemoglobin was 4 Gm. per 100 c.c., and the white blood count 8,000. The anemia was thought to be the result of general nutritional and iron deficiency. An evaporated milk formula supplemented with cereal, egg yolk, a preparation containing vitamins B and C, and elixir of ferrous sulfate were prescribed. After one week at home on this regimen, there was no improvement. The infant was then admitted to the hospital for further study.

The physical findings were unchanged except for a new pustular lesion on the occiput measuring 1 by 2 cm. A catheterized urine specimen contained a trace of protein and ten to twenty white cells in the sediment. Urine cultures yielded hemolytic and nonhemolytic *Escherichia coli*. Tuberculin and histoplasmin skin tests were negative. The serum proteins were 6.1 Gm. per 100 c.c., and with albumin 3.9 Gm. and globulin 2.2 Gm. The nonprotein nitrogen was 26 mg. per 100 c.c. and the serum bilirubin 1.1 and 2.2 mg. on different occasions. A roentgenogram of the chest showed enlargement of the heart and clear lung fields. Roentgen examination of the intestinal tract and long bones showed no abnormalities. Gastric analysis showed free hydrochloric acid in the gastric contents.

Examination of the peripheral blood (Table I) showed a severe normochromic, normocytic anemia with leucocytosis and thrombopenia. The red blood cells were well colored and varied greatly in size and shape. Stippled red cells, huge basophilic macrocytes, nucleated red cells of large diameter and with immature nuclei, nonsegmented neutrophils, neutrophilic myelocytes and myeloblasts were present in the circulating blood. Bone marrow aspirated from the tibia was very cellular and showed conspicuous megaloblastic development of the red and white cell series (Fig. 1, A). The erythroid elements were increased to predominate over the myeloid elements.

After admission to the hospital the infant remained listless, ate poorly, and vomited frequently. Parenteral fluids were administered but blood transfusions were withheld. Penicillin and sulfonamide therapy was given for the urinary tract infection which cleared in a few days. The blood values continued to fall and the infant became weaker and developed muscular twitching. She improved slightly when given oxygen therapy.

On the second hospital day a single dose of 0.002 mg. of vitamin B<sub>12</sub> was given intramuscularly. The reticulocyte percentage rose two days later and reached a peak of 69.1 per cent on the seventh day. A second bone marrow examination at this time showed the marrow still extremely cellular with erythroid elements predominating. A suggestion of megaloblastic development was still present. Following the reticulocytosis there was rapid regeneration of blood (Table I). A third bone marrow examination thirteen days after the injection

of vitamin B<sub>12</sub> showed normoblastic cellular development with very active red cell proliferation. The infant's condition improved rapidly with the gain in hemoglobin and red cell count, and when discharged two weeks after the vitamin B<sub>12</sub> injection, she was active, playful, eating well, and able to sit alone in bed.

She was brought back to the clinic for follow-up examination three and ten weeks after returning home. She had continued to eat well and had gained weight steadily. The blood values were normal (Table I).

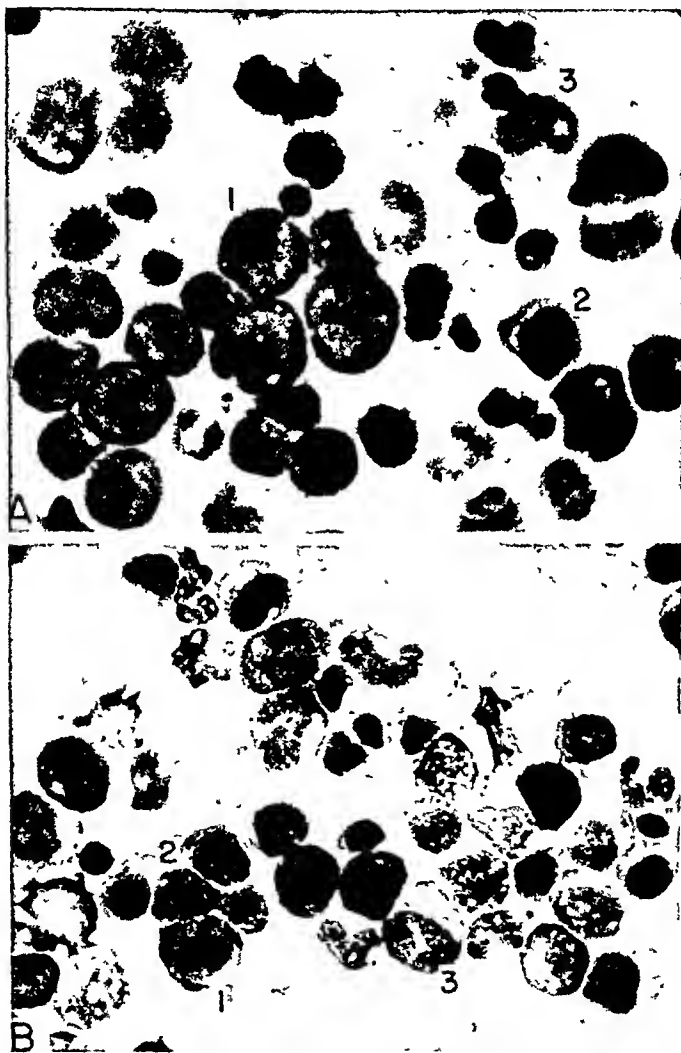


FIG. 1.—A. Photograph of bone marrow of patient in Case 1 before treatment ( $\times 625$ ). B. Photograph of bone marrow of patient in Case 2 before treatment ( $\times 625$ ). 1, Promegaloblast; 2, megaloblasts; 3, giant metamyelocyte.

CASE 2, W. J. P., C-44538.—This 7-month-old white male infant was admitted to Duke Hospital on Sept. 22, 1948, having had swelling of the legs and generalized weakness for two months

At birth the infant was healthy. He was fed a powdered milk formula with vitamin supplements. He grew well and weighed 14 pounds at the age of 14 weeks. About this time he developed a series of ulcerated lesions in his mouth and throat. He began to eat poorly and vomited frequently. It was necessary to admit him finally to the local hospital where anemia was discovered. He was given a blood transfusion and goat's milk was substituted for cow's milk in his formula. At home he was better for about three weeks but then again he began to eat poorly and lose weight. Swelling of his feet was noted from time to time.

The infant's parents and a 4-year-old brother were well.

Physical examination showed a serawny, weak, irritable, and chronically ill infant weighing 11½ pounds. He was not jaundiced. There were no local abnormalities about the head, neck, or chest. The liver and spleen were not palpable. There was slight edema of both feet.

Urinalyses, stool examination, and serologic tests for syphilis were negative. The tuberculin and histoplasmin skin tests were negative. The fasting blood sugar was 90 mg. and the nonprotein nitrogen 25 mg. per 100 c.c. The serum bilirubin was not elevated. The serum proteins were 3.9 Gm. per 100 c.c. with albumin 2.0 Gm. and globulin 1.9 Gm. There was no free hydrochloric acid in the gastric contents after histamine injection. Roentgen examination of the chest, intestinal tract, skull, and long bones showed no definite abnormalities.

Examination of the peripheral blood showed a normocytic normochromic anemia (Table II). In the stained blood films the red cells varied moderately in size. Many were obviously macrocytic. The differential white cell count included a small number of nonsegmented neutrophils. Bone marrow of high cellularity was aspirated from the tibia. In the stained films the predominant cells were large neutrophilic granulocytes showing maturation arrest at the late myelocyte stage. The erythroid elements had megaloblastic characteristics (Fig. 1, B).

The infant was given 0.002 mg. of vitamin B<sub>12</sub> intramuscularly and a week later 0.005 mg. A transient reticulocytosis occurred on the ninth day of therapy but the bone marrow remained megaloblastic and the blood values continued to fall (Table II). He continued to vomit in spite of several changes in formula, and gradually became very weak and listless. On the twelfth day the vitamin B<sub>12</sub> was increased to 0.002 mg. daily. Twenty grams of serum albumin were given intravenously during a four-day period. On the nineteenth day of anti-anemic therapy there was a second reticulocytosis which was better sustained reaching a maximum of 29 per cent on the twenty-fourth day (Table II). A third bone marrow examination showed a great increase in the percentage of erythroid elements predominantly normoblastic in morphology.

The infant began to eat normally, gained in weight and strength. Anti-anemic therapy was discontinued. He was discharged home thirty-two days after the beginning of treatment. The total serum proteins had risen to 6.9 Gm. per 100 c.c. with albumin 4.3 Gm. and globulin 2.6 Gm. In the stained blood films some of the red cells remained macrocytic. The bone marrow showed normoblastic cell development.

On a check-up examination six weeks later the infant was perfectly well to all outward appearances. He had continued to eat well and had gained 4 pounds in weight. The blood values were within range of normal (Table II). The bone marrow showed no abnormalities.

#### DISCUSSION

Megaloblastic anemia in infants is being recognized more frequently with the wider employment of detailed hematologic studies, especially bone marrow

TABLE II. HEMATOLOGIC FINDINGS IN CASE 2, W. J. P., C-44538

DATE 1948	Hb. (GM. PER 100 C.C.)	RBC (MILLIONS PER CU.MM.)	HEMATO-CRIT	RETICULO-CYTE (PER CENT)	DAY OF THERAPY	DIFFERENTIAL WBC AND THERAPY
9/24	10.9	3.1	29.5	1.3		Segmented polymorpho-nuclears 30, stabs 7, metamyelocytes 1, lymphocytes 58, mono-cytes 3, eosinophile 1.
9/25	<i>Tibial Marrow:</i> Segmented polymorphonuclears 4.5, stabs 33, metamyelocytes 23.5, myelocytes 12, myeloblasts 0.5, lymphocytes 4.5, eosinophiles 5, acidophilic megaloblasts 5.5, basophilic megaloblasts 9, promegaloblasts 2.5. Leucocyte: nucleated red cell ratio = 4.9:1					
9/27	10.2	3.1	28	1.1	0	Vitamin B <sub>12</sub> , 0.002 mg.
9/28				1.2	1	
9/29				0.4	2	
9/30				1.9	3	
10/1	9.5	2.9	26	2.2	4	
10/2				0.9	5	
10/4	9.2	2.8	25.2	3.2	7	Vitamin B <sub>12</sub> , 0.005 mg.
10/5				2.3	8	
10/6				31.7	9	
10/7				10.2	10	
10/8	8.9	2.8	26.8	5.9	11	
	<i>Tibial Marrow:</i> Megaloblastic erythroid development. Leucocyte: nucleated red cell ratio = 2.8:1					
10/9				3.1	12	Vitamin B <sub>12</sub> , 0.002 mg.
10/10					13	Vitamin B <sub>12</sub> , 0.002 mg.
10/11	7.7	2.5	22	5.0	14	Vitamin B <sub>12</sub> , 0.002 mg.
10/12				6.2	15	Vitamin B <sub>12</sub> , 0.002 mg.
10/13				6.6	16	Vitamin B <sub>12</sub> , 0.002 mg.
10/14				5.3	17	Vitamin B <sub>12</sub> , 0.002 mg.
10/15	7.7	2.4	21.2	4.7	18	
10/16				10.2	19	
10/18				18.7	21	Vitamin B <sub>12</sub> , 0.002 mg.
10/19	8	2.5	24.1	19.4	22	Vitamin B <sub>12</sub> , 0.002 mg.
10/20				24.6	23	Vitamin B <sub>12</sub> , 0.002 mg.
10/21				29	24	Vitamin B <sub>12</sub> , 0.002 mg.
	<i>Tibial Marrow:</i> Leucocyte: nucleated red cell ratio = 1.2:1					
10/22	10	3		16.7	25	Vitamin B <sub>12</sub> , 0.002 mg.
10/23				14.5	26	Vitamin B <sub>12</sub> , 0.002 mg.
10/24					27	Vitamin B <sub>12</sub> , 0.002 mg.
10/25				13.6	28	Vitamin B <sub>12</sub> , 0.002 mg.
10/26	10.9	3.3	32.5	10.9	29	Vitamin B <sub>12</sub> , 0.002 mg.
10/27				12.8	30	Vitamin B <sub>12</sub> , 0.002 mg.
10/28				11.2	31	Vitamin B <sub>12</sub> , 0.002 mg.
10/29	12	3.5	33	8.8	32	Vitamin B <sub>12</sub> , 0.002 mg.
	<i>Tibial Marrow:</i> Normoblastic erythropoiesis. Leucocyte: nucleated red cell ratio = 2.8:1					
12/7	12	3.9	37	2.8	71	
	<i>Tibial Marrow:</i> Leucocyte: nucleated red cell ratio = 3.8:1					

examinations.<sup>12</sup> Anemias developing in infancy during or following infection, or in association with feeding difficulties, are particularly suggestive of this entity. Our Case 1, apparently the first Negro infant reported to have this type of anemia,<sup>9, 12</sup> indicates that there is no real racial immunity. Some infants probably recover more or less spontaneously with treatment of infection, blood transfusions, general nutritional therapy, etc.<sup>2, 4</sup> Opportunities for early and specific treatment should not be overlooked, however, since eight of the twenty-five seriously ill infants reported by Zuelzer and Ogden<sup>12</sup> died of the anemia or its complications.

The megaloblastic anemia of infants is more comparable to nutritional macrocytic anemia in adults and the macrocytic anemia of sprue or idiopathic steatorrhea than to pernicious anemia. Only in the latter is histamine refractory gastric achlorhydria a constant feature. Pernicious anemia is distinguished, also, by an anemia showing hemolytic features, the frequent occurrence of serious neurologic manifestations, and the necessity for permanent antianemic therapy.

The quantitative response of the anemia to liver extract or pteroylglutamic acid has been variable. The reticulocyte rise is often slight and regeneration of red cells and hemoglobin slow. This is probably due to the gravity of the associated complications, particularly infection. Several weeks or repeated courses of therapy may be necessary before the anemia is corrected.<sup>8</sup> In our Case 1, an experiment in minimal dosage of vitamin B<sub>12</sub>, there was a prompt and dramatic hemopoietic response. In Case 2 more prolonged therapy was required. A quantitative regeneration of the entire erythroid series apparently occurred. The variable response of the anemia makes comparison of the relative effectiveness of different therapeutic compounds difficult. That vitamin B<sub>12</sub> is effective at all is of interest, for early reports indicate that minute amounts of the substance have the therapeutic activity of refined liver extract.<sup>10, 11</sup> In pernicious anemia vitamin B<sub>12</sub> has a nutritional value lacking in pteroylglutamic acid.<sup>8</sup> There is no definite evidence to indicate, however, that pteroylglutamic acid is not a completely effective compound in the treatment of megaloblastic anemia of infancy.

#### SUMMARY

Two infants, one a Negro, with megaloblastic anemia were treated with vitamin B<sub>12</sub>. Both responded favorably, one to a single injection of 0.002 mg. of the compound.

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# GLYCOGEN DISEASE OF THE LIVER

## WITH REPORT OF A CASE

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LONDON, ENGLAND

THOUGH glycogen disease of the liver was first described by Snapper and Van Creveld,<sup>21</sup> Von Gierke<sup>22</sup> reported two cases which came to autopsy, and his name has been given to this condition. The whole subject has been reviewed by Van Creveld.<sup>22</sup> The disease is characterized by the accumulation of excessive quantities of glycogen in the liver, kidneys, skeletal muscles, or heart. Deposits have also been found in the brain, and the blood glycogen has been found to be raised in some cases. The liver is most often affected, sometimes the kidneys also, as in Von Gierke's original two cases, and the skeletal muscles, but despite the enormous accumulation of glycogen no gross disturbance in the function of these organs results, except in the case of the heart, whose involvement alone has been described with heart failure in infancy. Mason and Andersen<sup>17</sup> would restrict the name of Von Gierke's disease to those cases in which the liver is predominantly involved; they stated that up to that date only thirty-four cases in which they considered the diagnosis to have been proved had been described. Crawford,<sup>6</sup> adding three cases of his own, mentions eight others. Since then, cases have been described by Schneider<sup>18</sup> (two cases). Abramson and Kurtz<sup>1</sup> (four cases), Bridge and Holt<sup>3</sup> (two cases), and Chieffi and Nassi<sup>4</sup> (three cases). Manter and Bowman<sup>16</sup> state that no cases were seen in Rhode Island Hospital between 1934 and 1942 in over 5,000 admissions. The condition, therefore, is a rare one, and partly on this account and partly because of some improvement with treatment, the following case is described.

### CASE REPORT

The patient, a male, was first seen at the Princess Louise Hospital for Children, London, on Nov. 1, 1938, at the age of 14 months, suffering from stomatitis. On routine examination hepatomegaly was discovered and he was admitted for investigation. The mother had been well throughout the pregnancy; the child, her first, was born at full term by normal delivery and weighed 7½ pounds at birth. He was breast fed for one year and had had no illnesses except for rubella. Milestones were normal. The mother had not considered his abdomen to be of excessive size. Mother and father were both alive and well and not related. No family illness was admitted.

*Examination.*—The child weighed 24 pounds. Ten teeth were present. Apart from stomatitis, the only abnormality noted was in the abdomen, which was distended and showed prominent upper abdominal veins. The liver was enlarged down to the umbilicus. The spleen was not palpable.

A glucose tolerance test (Fig. 2, Table I) was done, following the ingestion of 25 Gm. glucose. The Wassermann reaction was negative, icteric index

From the Paediatric Unit, St. Mary's Hospital, London, W. 2, England.

3, fecal fats 21.2 per cent with 81 per cent split, and the blood count was hemoglobin 70 per cent, red blood cells 3,860,000, white blood cells 5,500, and 72 per cent polymorphonuclears. There is no record of the urine having been examined for ketone bodies and neither an adrenaline response test nor an estimation of blood cholesterol was made.

The boy was kept in the hospital until the end of January, 1939. After the stomatitis cleared up he remained well, but the abdominal distention increased, and on discharge the liver was palpable 1 inch below the umbilicus and the abdominal circumference at the umbilicus was 22½ inches.

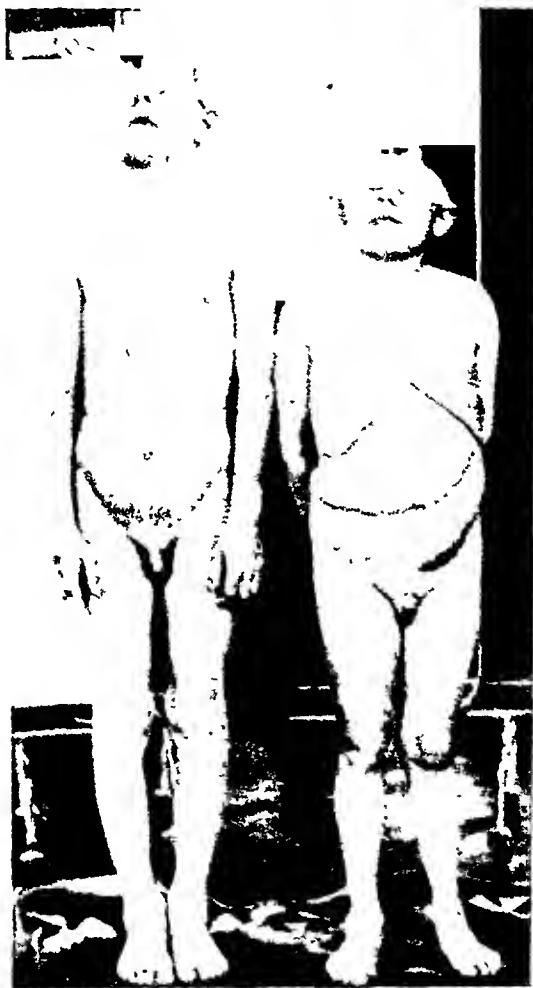


Fig. 1.—Patient with normal boy of same age.

He was seen in the outpatient department at intervals and remained well except for frequent coughs and colds. In March, 1939, he was described as flabby and he was said to tire easily. His weight was then 27 pounds and the abdominal circumference 27 inches. During this month he had a few episodes

of vomiting which were relieved by giving glucose. He was not seen for seven years after April, 1940, when neither the weight nor the size of the liver were recorded, but the abdominal distention was less and the circumference at the umbilicus was 25 inches.

He was next seen on June 11, 1947, at the age of 9 years, having been sent by his school doctor because of obesity. He had remained well since his last attendance and his school record was satisfactory. He was stated to be a big eater, especially of starchy foods.

TABLE I. ORAL GLUCOSE TOLERANCE TESTS (BLOOD SUGAR MG. PER 100 C.C.)

DATE	FASTING	½ HOUR	1 HOUR	1½ HOURS	2 HOURS
1/24/39	89	89	125	107	107
6/16/47	57	156	113	96	93
6/28/47	63	106	111	161	114

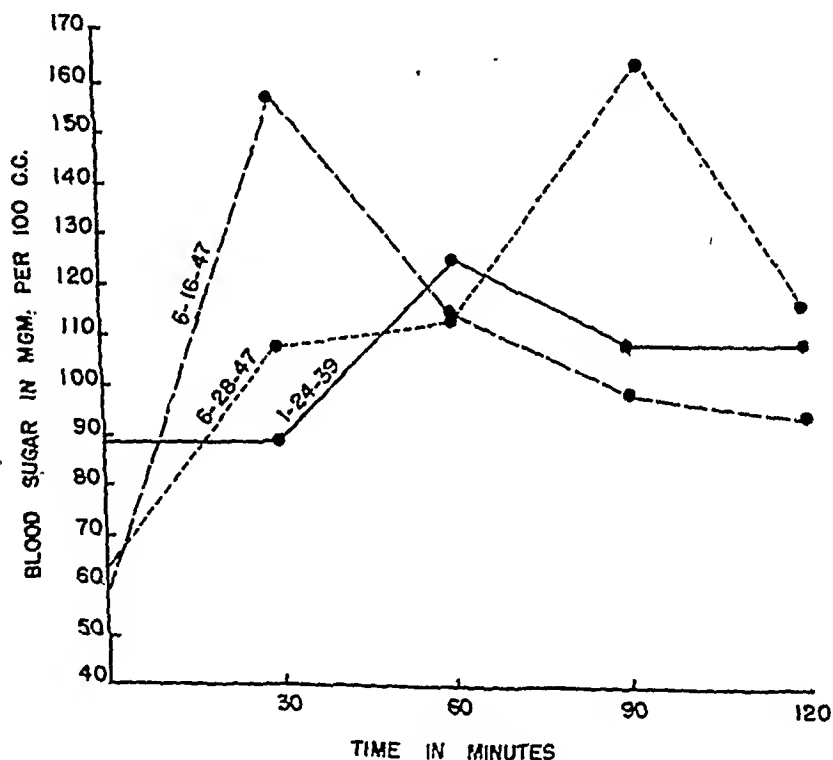


Fig. 2.—Blood sugar curves after oral glucose.

The family now included two brothers aged 3 years and 2 years. The liver of the younger was palpable one fingerbreadth below the costal margin in the nipple line, but the mother refused to allow further investigations to be carried out. She is a large, obese woman, while her husband is slightly below normal size. He maintains that in his youth his condition was similar to that of his eldest son and that he remained obese until the age of 23 years. Photographs of him at the age of 11 years bear out this, but it has not been possible to obtain any medical evidence of his past history. No clinical abnormality can now be detected and there is no ketonuria.

The patient was admitted to the hospital for investigation on June 11, 1947. His weight was 66 pounds (average for his age is 67 pounds) and height 47 inches (average, 52 inches). He was slow and deliberate in movement and in his mental processes, but his intelligence was normal for his age. The abdomen was protuberant and the circumference 32½ inches at the umbilicus. The liver was enlarged down to the umbilicus and was firm and smooth. The left kidney was palpable but not the spleen. The external genitals appeared small, but this could be largely due to the obesity.

The urine at all times of the day contained ketone bodies, detected by Rothera's but never by Gerhardt's test. The results of glucose tolerance tests done on June 16 and June 28, after 50 Gm. glucose, are shown in Fig. 2 and Table I, and of adrenaline response tests on June 17 and June 29 in Fig. 3 and Table II. The blood cholesterol was 260 mg. per cent. Wassermann reaction and Kahn tests were negative. Full blood count was normal and x-rays of skull, chest, and long bones were normal. A straight x-ray of the abdomen showed the kidneys to be slightly enlarged.

TABLE II. ADRENALINE RESPONSE TESTS (BLOOD SUGAR MG. PER 100 C.C.)

DATE	FASTING	15 MINUTES	30 MINUTES	MAX. RISE
6/17/47	57	60	56	3
6/29/47	58	64	54	6
1/21/48	38	47	59	21

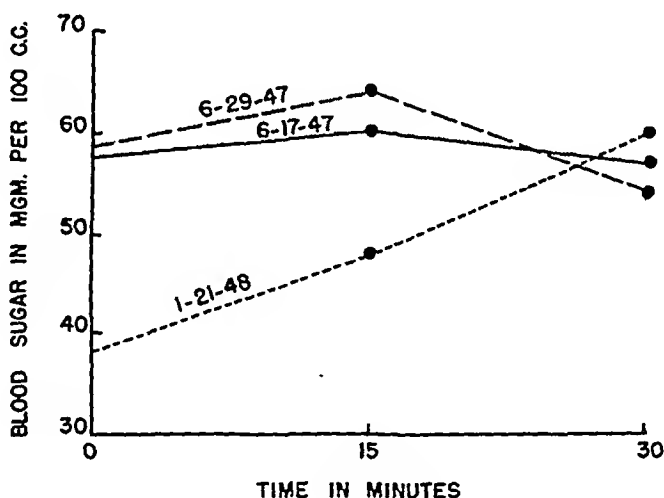


Fig. 3.—Adrenaline response tests (5 minims adren: HCl 1/1000, S.C.I.).

Treatment with Chonex tablets, one three times a day, was started on June 21, 1947, and the dose was increased to two tablets three times a day on June 25, 1947. (Each tablet contained 5 grains of dehydrocholic acid.)

Rothera's test, which was faintly positive on June 25, was negative in all specimens the next day and remained so until he was discharged on July 1, to continue taking two Chonex tablets three times a day. His weight was then 69 pounds.

He was seen in the outpatient department at intervals. There was no ketonuria in an early morning specimen in mid-July. However, when he next at-

tended at the end of October, ketone bodies were again detected in the urine but he had had no tablets for two and one-half months as he had not attended for a fresh supply. His weight was then 75 pounds. Chonex tablets were again given, and in December the mother thought he was more active. At the end of January, 1948, his weight was 75 pounds. The liver was still palpable at the umbilicus, but the abdominal circumference had decreased to  $29\frac{3}{4}$  inches. Rothera's test was positive, but the specimen tested was not passed until 11 A.M., and he had had no food that day. An adrenaline response test was performed (see Fig. 3).

*Discussion.*—There seems no doubt that this patient is suffering from glycogen disease of the liver, although the final proof would depend on a liver biopsy and this the parents refused.

Mason and Anderson<sup>17</sup> consider the essential features to be marked hepatomegaly without splenomegaly from early life, a tendency to ketosis, no hyperglycemic response to the injection of adrenaline, and a delayed fall in the blood sugar curve. Van Creveld<sup>22</sup> pays great attention to the adrenaline response, but considers it probably superfluous if ketonuria is already present. All Mason and Andersen's criteria are fulfilled by this case. The only alternative diagnosis would appear to be hypertrophic steatosis of the liver,<sup>8</sup> in which there is a gross accumulation of fat in the liver without evidence of any infection to account for it. The clinical features and prognosis of this condition and of glycogen disease of the liver are similar, and Debré<sup>7</sup> classifies them together as *hepatomegalie polyconique*; in his opinion differentiation is only possible by liver biopsy, although he agrees with Van Creveld<sup>22</sup> that hypercholesterolemia and ketonuria are not features of hypertrophic steatosis. Ketonuria was not a feature of the case of hypertrophic steatosis reported by Kraymer, Grayzel, and Solomon<sup>13</sup> and Van Creveld considered that the presence or absence of ketonuria differentiated the two conditions. Debré is unwilling to accept this as an absolute point of distinction, and considers that hypertrophic steatosis should be regarded as closely allied to glycogen disease, following it or preceding it, but most often combined with it. Personal observation has shown that certain patients with fatty livers, as well as those with livers filled with excess glycogen, show a low fasting blood sugar level, abnormal glucose tolerance curves, and lack of adrenaline response. It is also true that excess fat as well as glycogen may be found at autopsy in the livers of patients dying of glycogen disease, an observation first made in Von Gierke's original two cases and subsequently confirmed by others. As a general rule, glycogen and fat are mutually exclusive in the liver and it would appear desirable to separate the two conditions in which an excess of either is present. The evidence points to such a separation being possible by the presence of hypercholesterolemia and ketonuria in glycogen disease of the liver and not in hypertrophic steatosis.

Apart from infantilism which tends to be more obvious when the condition has been present for a number of years, glycogen disease of the liver is usually symptomless, but attacks of vomiting and a preference for carbohydrates (as in this boy) have been recorded previously. Obesity has been present in a number of cases

In 70 per cent of normal children the fasting blood sugar level lies between 75 and 100 mg. per cent.<sup>5</sup> In glycogen disease values below these levels are obtained and in the glucose tolerance test the essential feature is the delayed return to the fasting level. The curve may be high or flat and a diphasic type has been frequently noted.

Van Creveld<sup>23</sup> states that no treatment is effective. He did, however, abolish ketonuria in a case of glycogen disease by giving choline. The rationale of this treatment is that choline is a lipotrope and prevents deposition of fat in the liver which is the only source of production of ketone bodies: these are derived from the oxidation of fats. Deuel and associates<sup>9</sup> found that choline given to fasting rats after a high fat diet reduced the amount of ketone bodies in the urine as compared with controls, and MacKay and Barnes<sup>15</sup> obtained a similar result in fasting rats in whom ketonuria had been produced by injection of anterior pituitary extracts.

Bile salts were given to this patient because of the report by Linneweh<sup>14</sup> that during the administration of a bile-acid-lecithin compound over a period of three months to a patient suffering from glycogen disease, the liver had decreased in size: he had previously observed the disappearance of glycogen from frogs' livers in winter in an irrigation experiment with bile salts. Linneweh considered that these results were obtained by the action of bile salts in potentiating the activity of "liver diastase" by diminishing its fixation to the intracellular boundaries. Seckel<sup>19</sup> produced glycogenolysis in rats' livers in vitro by perfusing them with bile salts, and he postulated that the latter acted by virtue of their surface activity: he quotes Forsgren's observation that in adults and in animals a high bile acid secretion is associated with a low level of hepatic glycogen and vice versa. Although the steps in the breakdown of glycogen to glucose have now been worked out, it is not possible to explain how bile salts influence this reaction. Linneweh's explanation is at the least an oversimplification, since it is now believed that not one but a number of enzymes are involved in glycogenolysis.

Seckel,<sup>19</sup> Holt and McIntosh,<sup>12</sup> and Debré<sup>7</sup> refer to the treatment of glycogen disease by bile salts, but Linneweh alone appears to have actually used this treatment. It is of interest that temporary improvement has been recorded in two cases of glycogen disease during attacks of infective hepatitis. Anderson<sup>2</sup> noted a decrease in the ketonuria despite the fever, and Sundal (quoted by Holt and McIntosh) a diminution in the size of the liver.

With the administration of bile salts in this case there was a rapid disappearance of ketonuria, a decrease in the abdominal circumference of  $2\frac{3}{4}$  inches over seven months and no further gain in weight over a period of four months. It would be unwise to draw any conclusion as to the efficacy of treatment from the last adrenaline response test since, although the rise in the blood sugar level is more than that obtained previously, the results of the test are still not normal, as there should be a rise of at least 30 mg. per 100 c.c. in thirty minutes.<sup>10</sup>

Unfortunately it has not been possible to carry out further tests since the boy has not attended again, and repeated requests to the parents have been

fruitless. Their attitude is understandable, though regrettable, since they point out that the boy is in no way ill and the father believes firmly that the boy will recover spontaneously in the same way as he thinks he did himself.

No case of direct inheritance has been recorded, but familial cases have been described and Ellis and Payne<sup>10</sup> postulated the inheritance as a Mendelian recessive character. The history of the father of this boy is most interesting and raises much speculation.

It has been supposed that the prognosis is not good as there is an increased susceptibility to infections, but neither Van Crevelde nor Debré is in agreement with this. Certainly the prognosis would seem to be excellent in this boy. There are a number of reports in the literature of spontaneous cure at or about puberty. In Worster-Drought's case, in which puberty was delayed till 17 years of age, the liver which had extended 3 inches below the costal margin at the age of 10 years was no longer palpable at the age of 22, though acetone was present in the breath.<sup>21</sup> In Van Crevelde's first case, in the boy's middle teens the fasting blood sugar level rose, the ketosis lessened and the liver became smaller. Von Gierke (quoted by Van Crevelde) described a post-mortem examination on a girl of 15 years suffering from the disease, in which, although most of the liver presented the typical appearance, there were scattered areas of normal liver tissue. This was interpreted as possibly signifying commencing spontaneous recovery. Debré<sup>7</sup> records spontaneous cure at puberty in a patient of his own: he considers that patients tend to improve at puberty and become perfectly normal, but that this is not an invariable happening since some retain the stigmata of infantilism and enlargement of the liver. He states that even after the liver has returned to normal size the abnormal biochemical tests persist from some time, especially the presence of acetone in the breath and in the urine.

Apart from Worster-Drought's patient, all those whose cases are recorded in the literature are under 18 years of age and the majority are under 12 years old. This would suggest that spontaneous cure does occur since it is hard to believe that all died before adult life was reached.

The conception that spontaneous cure occurs at puberty is consistent with the hypothesis first advanced by Hertz<sup>11</sup> that glycogen disease is due to hypofunction of the anterior pituitary, since there is increased activity of the pituitary at puberty.<sup>20</sup> It is, however, necessary to postulate hypofunction of the pituitary-hypothalamic mechanism as does Debré,<sup>7</sup> since obesity of pure pituitary origin is due to increased activity of the anterior pituitary but may occur with hypothalamic lesions.<sup>20</sup> It is true that retardation of skeletal and sexual development, obesity, and increased sensitivity to the injection of insulin are common to glycogen disease and to hypofunction of the pituitary-hypothalamic mechanism, but it has been argued that these features in glycogen disease may be equally well explained by the disturbance of carbohydrate metabolism, that no pathologic changes in the pituitary have been found at autopsy (though it is agreed that there may be disturbance of function without demonstrable pathologic change), and that glycogen disease has not been reproduced in animals by



destruction of the anterior pituitary or hypothalamus; in fact, in experimental animals extirpation of the pituitary causes great diminution of the glycogen stores. Debré,<sup>7</sup> however, has brought forward further evidence: he quotes Képinov, who found that in the frog the glycogenolytic action of adrenaline was destroyed by removal of the pituitary but restored by the simultaneous injection of adrenaline and pituitary extract, and who postulated that glycogenolysis in the liver was dependent on the fixation of adrenaline on the hepatic cells by a pituitary glycogenotropic hormone. Debré also quotes work by Lamotte-Barrillion, who perfused the livers of hypophysectomized frogs with adrenaline and serum and obtained glycogenolysis when using serum from normal persons but not when using serum from patients suffering from glycogen disease; it was, therefore, concluded that in the latter a glycogenotropic hormone was absent from the serum. This work requires confirmation and, although it brings forward more cogent evidence in favor of a pituitary-hypothalamic disturbance, no improvement has been obtained in cases of glycogen disease by the injection of pituitary extracts.<sup>7</sup> The evidence, therefore, is, as yet, inconclusive.

#### SUMMARY

1. A case of glycogen disease of the liver is described.
2. Treatment with bile salts produced disappearance of ketonuria and decrease in the girth of the abdomen.
3. The diagnosis and prognosis are discussed.
4. The hypothesis that a pituitary-hypothalamic hypofunction is the cause of glycogen disease has recently received fresh support.

I wish to express my thanks to Dr. Ursula Shelley for permission to publish this case, to Mr. I. R. H. Kramer for carrying out the biochemical investigations, and to Dr. Reginald Lightwood for much helpful advice and criticism.

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# THE INFLUENCE OF ACUTE INFECTION UPON THE COURSE OF ALLERGY IN CHILDREN

## SOME CLINICAL OBSERVATIONS

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ANY consideration of the role of infection in the allergic child immediately raises the problem of bacterial sensitivity. Current observations in immunology demonstrate that either bacteria or bacterial products may produce tissue hypersensitivity with ensuing tissue changes which in most instances differ qualitatively from the pathology associated with nonbacterial hypersensitivity. In bacterial hypersensitivity fixed tissue changes are usually observed which are in distinct contrast to the reversible lesions resulting from edema seen with nonbacterial hypersensitivity. The identity of the mechanisms concerned with the two types of hypersensitivity has not been demonstrated. It is probable that bacterial sensitivity operates through a system entirely independent of the factors concerned with nonbacterial hypersensitivity, although it is likely that a single mechanism could operate in both instances with qualitative and quantitative variations in the tissue response, depending upon the nature of the antigen activating the system.

In addition to the ability of infection to produce a type of tissue hypersensitivity, clinical observations indicate that infection may play a role in the phenomena of allergy by influencing the clinical course of existing allergy. The purpose of this communication is to report on some clinical observations which demonstrate that a relationship does exist between infection and allergy in the child.

An allergic child with an acute infection presents a distinct pattern for his allergy. The pattern observed is one of two types, depending upon the nature of the infection. The first pattern is observed in association with pertussis, the infectious diseases—measles, chickenpox, and mumps, and the epidemic virus diseases. In these diseases the symptoms of allergy are aggravated during the period of invasion or the prodromal stage. During this stage, a child suffering with allergic rhinitis will have more severe nasal symptoms; the asthmatic child will have more severe asthma or allergic bronchitis; and the eczematous child will have an aggravation of his rash. As these acute infectious diseases approach their fastigium, there is a decrease in the severity of the symptoms of allergy. At the peak of the illness the child's allergy is at a lower level than he ordinarily experiences. Clinically he may be entirely free of the signs and symptoms of allergy. This stage corresponds with the paroxysmal phase of pertussis and the eruptive period of the infectious diseases. The child who had nasal symptoms of allergy will be entirely free; the

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asthmatic child will offer no pulmonary findings; the eczematous child will have a clear skin. With convalescence there is a recrudescence of the allergy, that is, with convalescence the signs and symptoms of allergy not only recur, but recur with greater severity and greater intensity than before the onset of the acute infectious disease. As will be observed in Fig. 1, which schematically illustrates allergy influenced by the named infections, a new base line has been established for the allergy. Prior to the infection the symptoms of allergy, though present, may be extremely mild and require little if

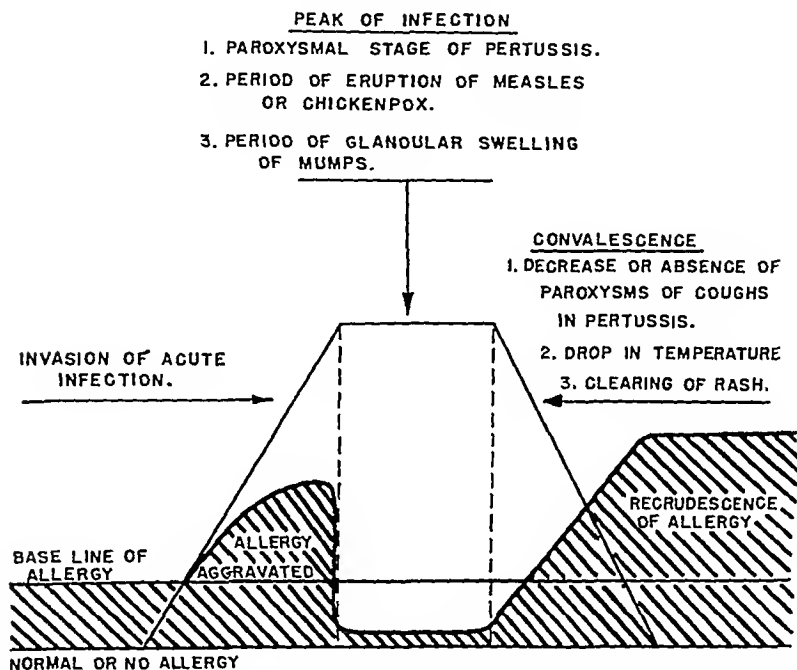


Fig. 1.—Schematic presentation of the influence of the acute infectious diseases upon the clinical course of allergy.

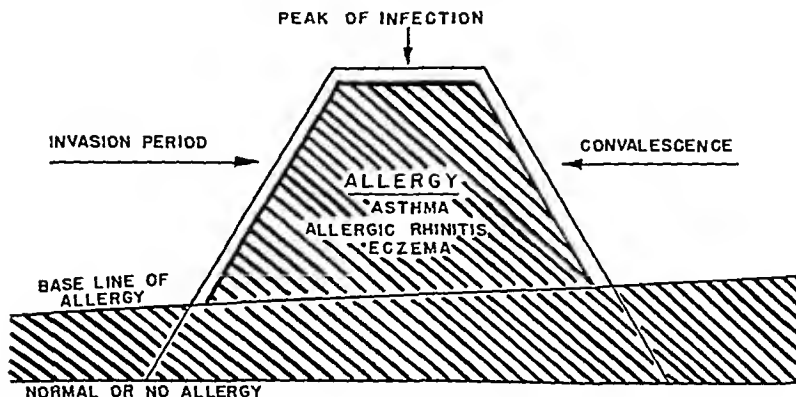


Fig. 2.—Schematic presentation of the influence of an acute upper respiratory infection (bacterial) upon the clinical course of allergy.

any medical management. Following the acute infectious process, the allergy becomes aggravated to such a degree that the child may experience his first attack of asthma. A mild eczema may become a severe eczema, or a mild rhinitis may present constantly annoying symptoms.

The second pattern is observed most commonly in association with acute infections of the upper respiratory tract, that is, rhinopharyngitis, acute tonsillitis with or without adenitis, adenoiditis, sinusitis, acute otitis, or any combination of involvement of the upper respiratory tract. In these infections there is no apparent change in the allergy during the period of invasion but at the height of the infection there is an aggravation of the allergy. Concomitant with the peak of the acute infectious process there is an aggravation of nasal symptoms or of the pulmonary symptoms which may be manifested by acute asthma or allergic bronchitis, or the rash of eczema may become more severe and itching is frequently more intense.

#### DISCUSSION

An analysis of some of the observations and attitudes on infection in the allergic child expressed in the literature in comparison with the two patterns presented raises some interesting points for discussion.

The exacerbation of allergy by measles is mentioned by Peshkin<sup>1</sup> who observed that asthma frequently recurred or was aggravated during the incubation period of measles, but with the appearance of fever the asthma cleared in the majority of these patients. No other such observation has been noted in the literature. The lack of further reports on the exacerbation of allergy during the invasion of an acute infectious process perhaps can be explained by its failure to occur as a constant finding. As the degree of aggravation of the allergy during this phase of the acute infectious process is usually not as severe as that seen following the disease, the clinician may overlook this observation unless he is alerted to the over-all pattern produced by an acute infectious process in the allergic child. In some cases, during the invasion of a contagious disease, the symptoms of allergy may return with greater violence and fail to respond to the usual medical management. With the establishment of the fastigium of the disease, the symptoms of allergy disappear completely. This observation is not peculiar to children. In a female, aged 37 years, whose asthma of many years' standing was controlled with a pollen antigen, the asthma suddenly recurred and persisted for ten days, when with equal suddenness the asthma cleared. The cough present since the onset of the asthma increased in severity and became paroxysmal. During this stage the chest was clear. The blood count revealed 12,000 leucocytes with 44 per cent polymorphonuclear leucocytes, 54 per cent lymphocytes, and 2 per cent monocytes. The diagnosis was pertussis. An almost similar history was experienced in an adult female, aged 28 years, whose asthma was under control. For one week prior to the establishment of clinical signs of epidemic parotitis the patient experienced a severe attack of asthma. Concomitant with the swelling of the parotid the asthma cleared.

Improvement of the signs and symptoms of allergy at the peak of an acute infectious process is also reported in the literature. Very early in the history of clinical allergy, Pirquet observed that a positive tuberculin may become negative during measles. In a discussion of desensitization, Rich<sup>2</sup> also points out "that the cutaneous reactivity to tuberculin often diminished markedly during the early stage of the exanthem of measles, to return again after a week or two. A similar diminution in reactivity has been observed during other acute infections." The clearing of eczema with measles is a common clinical observation. We have already noted Peshkin's<sup>1</sup> observations that asthma cleared with the appearance of fever of measles. Very little note has been made in the pediatric literature of the very important observation that a positive tuberculin becomes negative during the paroxysmal stage of pertussis, which was reported by both Galli<sup>3</sup> and Pospischill<sup>3a</sup> at about the same period that Pirquet reported on the tuberculin response during measles. The writer has questioned many clinicians, both pediatricians and allergists, and none can recall the occurrence of asthma during the paroxysmal stage of pertussis. Rackemann<sup>4</sup> states that when Allergy is well established, the effect of an intercurrent infection will depend upon its severity. An acute infection of relative severity, he states, may alleviate the allergy temporarily. The allergic child who gets measles will lose his eczema or asthma at the time of the intercurrent disease. Rackemann's opinion differs from our experience. The influence upon the allergic state is not related to the severity of the infection but the nature of the infection. The acute infectious diseases, measles, mumps, chickenpox, and pertussis, will show an improvement in the allergic state at the peak of the infectious process without relation to the severity of the infection.

In Case 1, reported later, illustrating eczema influenced by measles, the child suffered a modified measles following the administration of immune globulin. In Case 2 illustrating the influence of measles on the course of asthma, the child suffered with a severe reaction to his measles, but during the period of intense eruption his chest was clear and there were no symptoms of asthma.

In Cases 7 and 8 illustrating eczema influenced by chickenpox, one child suffered a severe infection with chickenpox while the other child had only a mild infection. These cases serve to illustrate that severity of the infection is not the influencing factor. With the acute infectious processes, regardless of the intensity of the infection, allergy will improve, while in the upper respiratory infections, allergy is aggravated at the peak of the infection. Here again, severity of the infection is not the determining factor. This would seem to indicate that the nature of the infection is the influencing factor rather than degree of infection.

The contention that fever is the determining factor when allergy improves during the course of an acute infectious process can be disclaimed by the same argument. During the course of the diseases mentioned in association with pattern 1, clinical allergy will improve without regard to the degree

of fever while in severe upper respiratory infections accompanied by high temperatures, even up to  $104^{\circ}$  or  $105^{\circ}$  F., the allergy may be aggravated. Fever may be a manifestation of an allergic response as is observed in serum sickness, the classical example of the acute allergic reaction or as has been more recently observed in penicillin reactions.

There is a difference in the immunologic responses in the two groups of infections as is evidenced by the fact that the first group calls forth a leucopenia or lymphocytosis in the blood picture, while the second group evokes a polymorphonuclear leucocytic response. The first group usually confers an immunity after a single infection while the second group confers no immunity. This immunologic difference between the two groups of infections is consistent with the observations reported by Bunting<sup>5</sup> and also Ehrlich and Harris.<sup>6</sup> These investigators state, "That the polymorphonuclear leukocyte does not play a part in antitoxic immunity seems to be indicated by a series of clinical observations which have been summarized in a general law of pathology to the effect that no disease which runs its course with a neutrophilic leucocytosis is followed by lasting immunity. A high lymphocytemonocyte ratio suggests resistance."

The aggravation of the allergic state by an infectious process as evidenced by the onset of the first attack of asthma is well recorded in the literature. Practically every modern text on either pediatrics or allergy cites the infectious processes as precursors in the onset of asthma and emphasizes the frequency of pertussis as an exciting agent.

In a study on the incidence and significance of various diseases and infections in asthma in children, Peshkin<sup>1</sup> pointed out the frequency of association of pertussis and measles with the onset of asthma. Walzer<sup>7</sup> states that among the common contagious diseases of childhood involving the respiratory tract, pertussis outstrips all others as an etiologic factor in asthma. Walzer also reports that a number of nonsensitive middle-aged asthmatics dated the onset of their asthma to the influenza epidemics of the last decade. Bray<sup>8</sup> observes that at least one out of each three cases of asthma that one sees will assign the onset to some infectious disease, and whooping cough and pneumonia are by far the commonest. Dienes<sup>9</sup> states that no doubt at times certain changes occur which predispose to sensitiveness. During infections such as whooping cough, that part of the system which makes antibodies is much more irritable. He believes that sensitiveness frequently follows infections. Rackemann<sup>4</sup> reported a similar attitude when he states that an acute infection irritates that part of the system which makes antibodies. Asthma may often begin after whooping cough, measles, or other acute infections. In reporting on prophylaxis in allergy, Ratner<sup>10</sup> also emphasizes the importance of measles and pertussis in antedating asthma. In a discussion on the etiology of asthma, Tuft<sup>11</sup> indicates the frequency of a history of pneumonia, influenza, or pertussis prior to the onset of the initial asthmatic attack. In his text *Allergy in Theory and Practice*, Cooke<sup>12</sup> expresses the opinion that, "A clinical history of an acute infection especially measles, pneumonia, influenza,

or bronchitis as the precursor of an allergy is obtained too frequently to be overlooked or to be rejected as of no moment. Infection as provocative of an allergy but not specifically and causally related to that allergy is an idea that must be investigated further." Cooke's statement is very pertinent. The infectious processes may not only play a definite role in the causation of clinical allergy but as illustrated by pattern 1 may have a distinct influence upon the course of the allergy. The occurrence of clinical allergy following an acute infectious disease is only one phase of the interplay between allergy and the acute infectious processes. The influence of the infectious processes upon the course of allergy raises many problems for investigation. Why is the alteration in the pattern of the allergic state by the infectious processes not a constant manifestation? In some cases the aggravation of the allergic state during the period of invasion may be observed with no recrudescence during or following convalescence. On the other hand, the exacerbation of clinical allergy following an acute infectious process may occur without any apparent influence upon the allergy during the phase of invasion. That this clinical observation is not uncommon is implied by the literature which frequently mentions the acute infectious processes as precursors of clinical allergy. The only constant observation is the improvement of the allergic state during the fastigium of the infectious diseases. Correlation of these clinical observations with immunologic studies would no doubt reveal the answers to some of these clinical phenomena.

The aggravation of the allergic state by the acute respiratory infections is generally accepted in pediatric practice and is cited frequently in the literature by observers reporting on infection in allergy. The allergy is most severe at the peak of acute infection. The allergic symptoms in association with this type of infection do not respond to the usual medical management for allergy. The best response is observed following the use of antibiotics, either sulfonamides or penicillin. As the infection subsides, the symptoms of allergy improve without any specific therapy directed toward the allergy.

#### CASE REPORTS

CASE 1.—M. S., a 14-month-old male child, was first seen on Jan. 20, 1948, with a complaint of generalized eczema. The eruption first appeared on the malar eminences a few days after birth. The rash became progressively worse involving both cheeks and the bends of the arms and legs, and soon after, the entire body was involved. The eruption was perennial showing no period of remission or improvement in any season of the year.

On physical examination the child had a temperature of 101° F. rectally. The development was good. The anterior fontanel was closed but the nutrition was very poor. All the symptoms were negative except the findings of the nose and skin. The nasal mucosa was pale and boggy and the turbinates were markedly edematous. There was a thin mucoid discharge on the floor of the nose. The skin of the entire body showed some involvement by an erythematous, dry, scaly eruption with a marked degree of secondary infection, folliculitis, and scratch marks. Over the scalp there was considerable dry exudate; itching was intense. All the superficial lymph nodes (cervical,

axillary, inguinal) were enlarged and doughy. A blood count at this time showed hemoglobin 69 per cent, erythrocytes 4,360,000, leucocytes 25,000 with 60 per cent neutrophils of which 52 were segmented, 29 per cent lymphocytes, 9 per cent monocytes, and 2 per cent eosinophiles.

Because of the marked infection, testing was delayed and treatment was directed against the secondary infection. Soaks in a solution of magnesium sulfate were instituted and 100,000 units of penicillin were administered every eight hours. The secondary infection subsided and the lymph nodes receded. The general condition of the skin showed a marked improvement. The torso was almost entirely clear and lesions of a nonexudative eczema were limited to the extremities particularly the flexural surfaces. The child was tested and was found extremely reactive to all the important environmental factors. In view of these findings the child was placed on a full diet with strict environmental control and treatment with an epidermal antigen. By March 12, 1948, the child's skin was completely clear, the lymph nodes had receded, nutrition had improved, and the child's well-being was excellent.

On March 24, 1948, the child was exposed to measles. One week later, March 31, he received human immune globulin. April 1, the child again showed a few small eczematous lesions in the flexural folds of the arms and legs. On April 4, the child experienced his first attack of asthma which responded to adrenalin. On the following day, his temperature rose to 101° F. rectally. On April 7, his temperature rose to 103.5° F. rectally and the exanthem of measles appeared. With the appearance of the rash the eczema cleared. There were no chest findings. On April 9, the child was fever-free. The evening of the same day the rash of eczema recurred on the face, arms, back of the neck, and the shoulders. When seen on June 17, the skin was entirely clear except for a few small excoriated lesions in the bends of the forearms. On August 12, the skin was entirely clear.

*Note:* This case illustrates the influence of measles in the course of allergy. The child experienced his first asthma with invasion of his measles. The eczema recurred at the same phase of the infection, cleared with the rash, and then recurred with convalescence. The influence on the allergy occurred although the child had a very mild case of measles.

CASE 2.—L. J., a 4-year-old child, was first seen on Aug. 4, 1947, with a complaint of eczema and asthma. The eczema appeared shortly after birth, involving the flexural surfaces of the arms and legs and the buttocks and had never cleared since its first appearance. There were no seasonal variations.

In April, 1945, the child had his first attack of asthma. The asthmatic attacks were preceded by itching of the nose, sneezing, and a watery discharge, followed by coughing and wheezing of two days' duration. The asthma was worse in the summer, but the cough was a perennial symptom.

On physical examination, the nasal mucosa was very pale and boggy, and the turbinates were edematous. There was a clear mucoid discharge on the floor of the nose. The tonsils were moderately enlarged and pale. There was no lymphoid studding of the postpharyngeal wall. The uvula was edematous and there was considerable postnasal drip. The cervical nodes were not enlarged. The chest was symmetrical. Movements were free and equal. On auscultation the breath sounds were harsh in character with prolongation of the expiratory phase. There were numerous coarse rhonchi intermingled with sonorous and sibilant râles. The heart was negative. The skin showed a dry, scaly, erythematous eruption with scratch marks limited to the flexural surfaces of the extremities. A nasal smear was positive for eosinophiles and pus



cells. On intradermal testing, the child reacted strongly to many important foods, the common environmental factors, and all the important pollens of Southern California. The child was managed by a strict environmental control, omission of the important food factors, and rotation of the diet combined with treatment with a pollen antigen which he started on Nov. 5, 1947. By Feb. 26, 1948, the child showed a definite improvement. The eczema cleared and he suffered only an occasional mild asthmatic attack. Between attacks the chest was clear. On June 23, 1948, the child was exposed to measles. On July 1, examination of the chest revealed a few rhonchi and sibilant râles. He was given 2 c.c. of immune globulin. On July 7, the child had an attack of severe asthma which responded only temporarily to 0.4 c.c. of adrenalin. Koplik spots were observed on the buccal mucosa. On July 9, the child's temperature rose to 104° F. rectally. The exanthem of measles appeared. With the appearance of the rash the chest cleared and remained clear throughout the period of the acute illness. As the rash cleared, the chest findings and respiratory symptoms recurred. The eczema, which had cleared, recurred and was of greater intensity than at the time of the child's first observation in August, 1947. Under continued allergy management both the pulmonary symptoms and the eczema showed improvement.

*Note:* This case illustrates the influence of measles on the course of asthma. In this case, the measles was severe as contrasted with the illness in Case 1.

CASE 3.—C. S., a 7-year-old female child, was first seen on Dec. 12, 1946, with a complaint of asthma. The history dated back to the age of 2 years when the child suffered with frequent head "colds," with a running and blocked nose accompanied by a paroxysmal cough lasting for several weeks at a time. In 1944, the patient had a tonsillectomy and adenoidectomy following which there was an improvement in symptoms for three months, after which period the cough returned. In April, 1946, the first wheezing was noted. This was accompanied by cough, difficult and rapid breathing with an elevation in temperature. Attacks occurred about every month lasting for three days and were usually nocturnal in character. For two weeks prior to the time of her first visit the child had asthmatic attacks every night and was comparatively free from symptoms during the day. On December 10 and 11, 1946, the child suffered with asthmatic symptoms which occurred both day and night. All attacks were preceded by a blocked nose and a dry cough.

On physical examination the child was well developed and fairly well nourished. The conjunctivae were injected. The nasal mucosa presented a bluish pallor; the turbinates were very edematous producing obstruction on both sides of the nose. The tonsils were absent. There was no regrowth of the lymphoid tissue. There was no cervical adenopathy. The chest presented no deformities. Respiratory movements were normal. Resonance was not impaired and on auscultation many coarse and sibilant râles were heard both anteriorly and posteriorly. Expiration was prolonged. The heart, abdomen, and skin were negative. A nasal smear was positive for eosinophiles.

On intradermal testing the child reacted to all the important environmental factors and the common local pollens. Management consisted of environmental control and treatment with both a pollen and an epidermal antigen which were started on Jan. 21, 1947. The response was good; the child's symptoms were controlled. The child was free from asthma until March 26, 1947, when she developed an acute attack of asthma lasting for three days after playing with a dog and rabbits. Her symptoms were again under control by removing the environmental factors. The child was symptom-free until May 21, 1948, when she developed acute asthma which did not respond to the

usual medical management (saturated solution of potassium iodide, ephedrine hydrochloride, theophylline, ephedrine, phenobarbital combined, and adrenalin hydrochloride 1-1,000). On May 28, 1948, the child had a temperature of 101° F. orally. At that time Koplik spots were observed on the buccal mucosa. The child had a harassing cough and had difficulty in breathing. Examination of the chest revealed scattered rhonchi and sibilant râles distributed both anteriorly and posteriorly throughout both lung fields. Expiration was prolonged. The symptoms showed a marked response to 0.4 c.c. of adrenalin but recurred within a few hours. On May 29, 1948, the exanthem of measles appeared and with the appearance of the rash the respiratory symptoms improved and the chest showed clearing. The chest remained clear for one week after the rash faded when the asthma recurred with coughing, labored respiration, recurring rhonchi, and wheezes. Since her measles, the child suffered intermittent asthma until Oct. 8, 1948, when she again showed improvement. Her asthma was again under control.

*Note:* This case illustrates the influence of measles on the course of asthma. Recrudescence does not always coincide with clinical convalescence. In this case asthma recurred one week after recovery from measles.

CASE 4.—L. T., a female child 6 years of age, was first seen in the Allergy Clinic of the children's Hospital on May 21, 1948, with a complaint of asthma since the age of 2 years. There was a history of eczema in early infancy which persisted until 2 years of age. The first asthma occurred almost immediately after the eczema cleared. The attacks of asthma which were characterized by labored respiration, coughing, and wheezing were about three days in duration, and were ushered in by running nose, sneezing, and coughing. The attacks were relieved by adrenalin. During the interval between the asthmatic attacks, the child suffered with sneezing in the morning, a running nose, and a loose productive cough which was worse at night. In February, 1948, the patient was hospitalized with a diagnosis of "bronchopneumonia" and asthma which responded to hydration and penicillin. Two weeks prior to the first clinic visit, the child had chickenpox with complete disappearance of her symptoms of allergy during the period of eruption with recurrence of asthma one week after convalescence. On physical examination the child was well developed, but poorly nourished. The palpebral conjunctivae were granular and pale. The nasal mucosa was pale and boggy. There was considerable mucoid discharge. The chest was symmetrical and the movements were free. The lungs were filled with coarse rhonchi and asthmatic wheezes. No dyspnea was observed. The heart, abdomen, and skin were negative. A diagnosis of asthma and allergic rhinitis was made.

The child was submitted to routine skin testing. On June 28, 1948, during the period of testing, the child developed a temperature of 100.4° F. rectally and showed a macular eruption of the pharynx with Koplik spots on the buccal mucosa with scattered rhonchi and squeaks throughout the chest. On July 1, the child developed an exanthem of measles simultaneously with which the respiratory symptoms improved, the lungs became clear and remained clear for two weeks after convalescence when the asthma recurred with attacks occurring practically every night. The lungs were constantly filled with rhonchi and asthmatic squeaks.

On July 22, 1948, skin tests were resumed. The child reacted strongly to intradermal tests with the environmental factors. Accordingly, environmental control was outlined and an epidermal antigen was started on Aug. 19, 1948. The child reacted with asthma to even doses of .05 c.c. of a 1:500,000 dilution. Intradermal therapy was started. Treatment was commenced with

.025 c.c. of 1:500,000 dilution intradermally increasing gradually by weekly intervals to 0.1 c.c. of 1:500,000 dilution. When the child reached a level of 0.1 c.c. of 1:500,000 dilution intradermally the child showed control of her asthma.

*Note:* This case illustrates the influence of both chickenpox and measles on the course of asthma. The child was symptom-free for two weeks after recovery from measles; when asthma recurred it was more severe and more constant than prior to the measles.

CASE 5.—R. B., a 10-year-old male child, first attended the Allergy Clinic on April 12, 1948. The patient was a very mild spastic, mentally-retarded child with congenital heart disease. During the first year of life he suffered a mild eczema following which he developed a severe allergic rhinitis which was perennial in character. In August, 1948, the patient developed measles which was preceded by an aggravation of the nasal symptoms producing almost complete nasal obstruction. During the period of the exanthem he was able to breathe freely through his nose which he had been unable to do for several years. One week following the measles the nose again became blocked with a severe allergic rhinitis. Skin testing revealed significant reactions to environmental factors.

*Note:* This case demonstrates the influence of measles upon the course of allergic rhinitis.

CASE 6.—J. C., a male child 6½ years of age, was first seen on July 9, 1946, with a complaint of asthma since 2 years of age. Following the onset of the asthma, the child had attacks about every two or three months of two to three days' duration. The attacks were characterized by sneezing, running nose, coughing, wheezing, and labored respiration. The symptoms were perennial with no seasonal changes.

He suffered itching of the eyes and injection of the conjunctiva. The nose was stopped perennially and was accompanied by itching, sneezing, and a clear mucoid discharge. He was subject to occasional upper respiratory infections with swelling of the cervical glands.

On physical examination the child was well developed and fairly well nourished. There was scaling of the palpebral margins and granulation of the palpebral conjunctiva. The nasal mucosa was pale and boggy with considerable mucoid discharge. The tonsils were small. The postpharyngeal wall showed a moderate degree of lymphoid studding. There were enlarged cervical nodes bilaterally. Examination of the lungs revealed normal breath sounds with a few coarse rhonchi scattered over both sides. Otherwise the physical examination was negative.

On intradermal testing, the patient reacted strongly to pollens and environmental factors and a few foods—cow's milk Casein, string beans, banana, and peanuts.

During the winter of 1947, the child was treated with a pollen antigen, strict environmental control, and elimination of the positive food factors. During this period he suffered with repeated attacks of upper respiratory infections accompanied by temperatures of 101° F. to 103° F. orally. During the infection, the cervical nodes became swollen and the child suffered with severe asthma. The asthma responded only temporarily to adrenalin (0.4 c.c. 1:1,000 adrenalin hydrochloride) but showed a good response to treatment with the antibiotics.

After Feb. 24, 1947, he had no upper respiratory infections, but the cervical nodes remained large. Attacks of asthma occurred less frequently.

Between May 26 and June 23, 1947, he was entirely free from asthma. On June 7, 1947, a tonsillectomy and adenoidectomy were performed. Following surgery the child showed a marked improvement—his appetite increased, his nutrition improved, and by Oct. 24, 1947, he showed a gain of 11 pounds in weight. He was free of asthma until October 27, when he again developed intermittent attacks of asthma which failed to respond to the usual medication. Coughing became paroxysmal, was worse at night, and was accompanied by flushing of the face and vomiting. Between November 10 and November 26, the paroxysmal nature of the cough became more evident but the chest was clear and the child suffered no asthma. On November 10 a blood count revealed 34,750 leucocytes of which 74 per cent were lymphocytes. On November 26, the count was still 17,100 leucocytes with a definite increase in lymphocytes. By December 19, the paroxysmal cough had subsided.

On Jan. 15, 1948, the child complained of paroxysms of sneezing with slight fullness of the nose. On physical examination the nasal mucosa, which during the period of the paroxysmal cough appeared normal, now presented a pale boggy appearance with considerable mucoid discharge. Examination of the lungs revealed scattered wheezes but there was no dyspnea. From that date the child suffered a recurrence of his asthma.

*Note:* This case illustrates the influence of pertussis upon the course of asthma. Although the child had severe paroxysms of cough, the chest remained clear during the height of the infection.

**CASE 7.**—R. D., a male child 4 years of age, was first seen on Jan. 9, 1946, with a history of eczema since 3½ months of age. The eruption was erythematous, sealy, and exudative with intense itching involving the face and entire body but most intense on the arms and legs especially the flexural folds of the arms and legs. The rash was perennial with no periods of remission. There was no history of wheezing but there was some sneezing and itching of the nose.

On intradermal testing the child reacted chiefly to the environmental factors. Under environmental control and treatment with an epidermal antigen, the eczema cleared by April 26, 1946. The skin remained clear until Dec. 18, 1947, when the eczema recurred on the extremities. Ten days later, the child developed a temperature of 100.8° F. rectally. The eczema cleared and lesions of chickenpox appeared. On Jan. 8, 1948, the chickenpox started clearing and five days later, eczema recurred involving the extremities accompanied by intense itching.

*Note:* This case illustrates the influence of chickenpox on the course of eczema. The illness with chickenpox was mild. Temperature was never over 100.8° F. rectally, and the eruption was of moderate degree.

**CASE 8.**—W. D., a male child aged 14 months, was first seen on Nov. 17, 1947, with eczema involving the legs and arms, flexural folds of all extremities, and the face. Eruption was dry, sealy, nonexudative, and very itchy. Except for nasal itching there were no respiratory complaints. During the winter of 1947 he had some mild wheezing and cough and also six upper respiratory episodes without fever which were diagnosed as allergic rhinitis.

The child was tested and reacted chiefly to the environmental factors. He was placed on strict environmental control and treatment with an epidermal antigen with a good response of his skin condition. On Dec. 17, 1947, the eczema became aggravated presenting for the first time considerable exudate, crusting, pustules, and edema. He failed to respond to routine management. On December 28, the child developed a temperature of 103° F.

rectally. The eczema was practically entirely clear and lesions of chickenpox appeared. Then there was intense itching of the lesions of chickenpox. On Jan. 5, 1948, the chickenpox cleared immediately following which the eczema recurred and presented a degree of severity equaling that just prior to the establishment of the chickenpox.

*Note:* This case illustrates the influence of chickenpox on the course of eczema. In contrast with Case 7, this child suffered a severe chickenpox with temperature elevated to 103° F. rectally and a very diffuse eruption of chickenpox. Cases 7 and 8 demonstrate that severity of infection is not the determining factor in influencing allergy.

CASE 9.—B. B., a 4-year-old female child, was first seen on Feb. 10, 1947, with a complaint of nasal itching, sneezing, and constant mucoid discharge. For a month preceding her initial visit, the child suffered redness and itching of the eyes. The symptoms were perennial with definite seasonal exacerbations beginning in April and continuing in July and then recurring in September.

On physical examination the conjunctivae were injected. The nasal mucosa was pale with turgescence. The turbinates were edematous. The tonsils were moderately enlarged but smooth. The uvula was edematous. There was considerable postnasal drip. Heart, lungs, abdomen, and skin were negative. A nasal smear showed a moderate number of eosinophiles and pus cells. On intradermal skin testing, the child showed strong reactions to chicken and goose feathers, cattle and dog hair, and house dust, as well as the important local pollens. Environmental control was advised and treatment instituted with a pollen antigen.

The child showed excellent control of her symptoms to the above management. Beginning on Feb. 22, 1948, the child developed severe symptoms of allergic rhinitis with nasal itching, considerable stoppage, and mucoid discharge. The lesions of chickenpox appeared. During the acute stage of the infection which lasted three days with temperatures between 102° F. and 102.6° F. rectally, the child was free of nasal symptoms. During the convalescence from chickenpox the nasal symptoms recurred accompanied by a cough. At this time her chest was clear but the nose presented a typical picture of allergic rhinitis.

*Note:* This case illustrates the influence of chickenpox on the course of allergic rhinitis. In this case the chickenpox was mild.

CASE 10.—R. F., a male child 7 years of age, first attended the Allergy Clinic at the Los Angeles Children's Hospital on Oct. 8, 1948, with a history of measles and chickenpox at 18 months and the onset of eczema, asthma, and allergic rhinitis at 2 years of age. All the symptoms were perennial showing no seasonal variations. At the age of 6 years, the child developed mumps with severe asthma preceding and following the parotid swelling, but was symptom-free during the parotid swelling. The eczema which had cleared since 5 years of age was uninfluenced by the parotitis.

*Note:* This case illustrates the influence of mumps on the course of asthma producing the typical pattern indicated in Fig. 1.

CASE 11.—B. H., a female child 16 months of age, suffered with a mild allergic rhinitis since 3 months of age. She suffered frequent attacks of sneezing, itching, with clear watery discharge. The symptoms were perennial with no seasonal variations. On physical examination there were no findings except a very pale edematous nasal mucosa with edema of the turbinates

and a clear mucoid discharge. On testing the child showed positive reactions to all the important environmental factors. She was treated with an epidermal antigen plus strict environmental control to which she showed a good response.

On Feb. 23, 1948, she had a recurrence of her nasal symptoms which persisted until February 27, when the child developed a temperature of 103° F. rectally with complete disappearance of nasal complaints. The temperature fluctuated between 103° F. and 104° F. rectally for four days. During this period the physical examination was essentially negative. The nose was clear. On March 1, her temperature dropped suddenly following which she developed a generalized fine macular morbilliform rash. A diagnosis of roseola infantum was made. A blood count done during the course of the acute illness was as follows: Erythrocytes 6,960,000, hemoglobin 74 per cent or 12.7 Gm., leucocytes 3,000 with polymorphonuclear leucocytes 26 per cent, lymphocytes 78 per cent, and monocytes 4 per cent.

On March 3, 1948, the symptoms of allergic rhinitis recurred. On examination the nasal mucosa was again pale and boggy and the turbinates were edematous. There was considerable thick grayish mucoid discharge on the floor of the nose. With continued therapy, the child's symptoms were again brought under control.

*Note:* This case illustrates the influence of roseola infantum on the course of allergic rhinitis. The writer has observed the same influence by roseola infantum on the course of allergic dermatitis (eczema).

#### SUMMARY

1. An acute infection in an allergic child may produce one of two patterns for the allergy depending upon the nature of the infection.

2. The first pattern is observed in association with pertussis and the viral infections including measles, chickenpox, mumps, Kaposi's disease, and epidemic virus infections.

3. The second pattern is observed in association with upper respiratory infections accompanied by a polymorphonuclear leucocytosis.

4. The group of diseases which produce the first pattern usually confer an active immunity after a single attack and their blood picture is a leucopenia, with the exception of pertussis which evokes a lymphocytosis. The infections which produce the second pattern confer no immunity and call forth a polymorphonuclear leucocytosis.

5. The improvement in clinical allergy by the one group of infection and the aggravation of clinical allergy by the second type of infection may suggest some studies in immunology to explain the variation in the allergic response. Such observations may help clarify the interrelationship between infection and allergy and reveal data explaining the underlying mechanisms.

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## HYALURONIDASE IN PEDIATRICS

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ONE of the newer products that has given promise as a therapeutic agent is hyaluronidase.\* This was first described as a spreading factor<sup>1, 2</sup> in 1929 and later identified as a mucolytic enzyme.<sup>3-6</sup> It has been obtained from numerous sources including bacteria, bee, snake, and spider venoms, leech extracts, spermatozoa, and mammalian testes.

Observations regarding its role in infection and fertilization have been formulated. Now its place in increasing fluid absorption is being investigated. The latter action has been explained by the fact that hyaluronidase is a mucolytic enzyme<sup>3</sup> which acts on and depolymerizes the mucopolysaccharide, hyaluronic acid. This is the gel present in the ground substance of connective tissue and acts as a tissue barrier to fluid diffusion.

With the aid of this enzyme, it has been shown<sup>7</sup> that fluid absorption could be increased twelvefold. In our recent report,<sup>8</sup> it was demonstrated that absorption was facilitated by a multiple varying from five to fourteen. The solutions used varied from normal saline, glucose in saline, Hartmann's and Ringer's solutions, to penicillin, streptomycin, adrenalin, and procaine, and the results were consistent throughout. Hyaluronidase was also tested on patients with various acute infections with elevated temperatures, and on those with allergies and with rheumatic fever, but its effect remained unchanged.

To determine its range of safety, six individuals were studied from the standpoint of its effect on urine, urine excretion, blood count, sedimentation rate, cholesterol, phosphorus, phosphatase, proteins, urea N, creatinine, sugar, ieterie index, van den Bergh, and cephalin flocculation. In addition, sixteen other cases were studied in their relation to urinary and cephalin flocculation changes after daily injections of the enzyme. As far as could be determined,<sup>8</sup> no detectable alteration in body physiology was observed.

Skin-testing for allergic manifestations was done with the first of the products obtained, and of seventy-nine children, seven were sensitive, while of twenty-nine adults, three were positive. At that point,<sup>8</sup> it was felt that impurities in the product might be an explanation for this.

With our second product, there were only eight positives out of 475 cases, and when 122 (including seven of the previous allergies) were retested one month later, only two remained sensitive. The following month, only one positive was noted, and three months later out of forty that were rechecked (including the previous positive) not one allergic reaction was obtained.

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Recently a more highly purified product was received and to date 105 adults and 158 children have been skin-tested with only one child revealing an allergic response. This child was negative one month before and now is sensitive to both an intradermal and subcutaneous test.

(Conjunctival tests were performed on forty infants under 1 year of age, on eleven children from 4 to 12 years (including the previous positive reactor), and on fourteen adults. Not one sensitivity was observed with readings at fifteen and thirty minutes and also at one and twenty-four hours. This interesting result, although not conclusive since it was only noted in one case, indicated that the skin test appeared to be more sensitive than the eye test.

In summarizing these results (Tables I and II), there have been 1,048 skin tests with twenty-two positives for a 2.1 per cent with the probabilities that the figure will be reduced as more tests are done with the latest purification of the product.

TABLE I. HYALURONIDASE SKIN TESTS

	FIRST GROUP	SECOND GROUP	THIRD GROUP	TOTALS
<i>Adults</i>				
Number	29		105	134
Number positive	3		0	3
Per cent positive	10		0	2.2
<i>Children</i>				
Number	79	475	112	666
Number positive	7	8	0	15
Per cent positive	8.9	1.7	0	2.3
<i>Tests Repeated</i>				
<i>1 Month</i>				
Children		122	46	168
Number		(Included 7 previous positives)		
Number positive		2	1	3
Per cent positive		1.6	2.2	1.8
<i>2 Months</i>				
Children		40		40
Number		(Included 2 of previous positives)		
Number positive		1		1
Per cent positive		2.5		2.5
<i>3 Months</i>				
Children		40		40
Number		(Included previous positive)		
Number positive		0		0
Per cent positive		0		0
<i>Totals</i>				
Number	108	677	263	1,048
Number positive	10	11	1	22
Per cent positive	9.3	1.6	0.4	2.1

TABLE II. HYALURONIDASE CONJUNCTIVAL TESTS

	UNDER 1 YR.	4-12 YR.	ADULTS	TOTAL
Number	40	11	14	65
Number positive	0	0	0	0
Per cent positive	0	0	0	0

Once the harmlessness of hyaluronidase was verified, clyses utilizing it were started and to date we have used it in fifty cases. Each one received from 40 to 320  $\mu$ g depending directly on the duration and severity of the case. When hyaluronidase was given, the same area could be used with good absorption even up to five days. It worked best during the first clysis with gradually diminishing effect as others followed. When given over the medial aspect of the thighs, some patients developed edema of the scrotum which quickly subsided with the absorption of the fluid.

In the average case, 250 to 300 c.c. of electrolytic solution could be rapidly given within eighty minutes when utilizing hyaluronidase and other clyses could be given in fairly rapid succession. Previous to its use, a similar clysis took 150 to 180 minutes and the area could not be used again for about eight hours. Thus its use should result in quicker fluid correction and greater amount of fluid absorption per unit of body area.

In estimating the probable capacity of hyaluronidase, it was found that each microgram could take care of from 10 to 50 c.c. of electrolyte solution. The same area was used for as long as eight days in one case, but rarely was it necessary to continue for that length of time. The needles were kept in one position for five days in two cases, four days in six cases, and three days in four cases, with the remainder being in place for 1 or 2 days. Since the tissue became inflamed around the point of insertion of the needle, after the second day in most cases, it was deemed advisable to change its site every third day, but the same area could still be used if necessary.

Increasing the dose of hyaluronidase did not increase its effect in proportion to its increment. This was demonstrated in five patients, who were each given 150 c.c. of 5 per cent glucose in saline in each thigh. The comparison was made between a 20  $\mu$ g dose on one side and a 40, 80, 100, 200, and 300  $\mu$ g dose, respectively, given on the opposite side. In each one, the fluid was run in within one hour and while absorption was complete in sixty minutes on the 20  $\mu$ g side, it took only forty-five minutes on the 40  $\mu$ g side and twenty-five to thirty-minutes on the 80, 100, 200, and 300  $\mu$ g sides, indicating that it would be wasteful and nonbeneficial to increase the dose above 80  $\mu$ g per area per dose.

In addition, plasma was given subcutaneously in seven cases with gratifying results. First a volunteer was given 50 c.c. of plasma in one thigh and another 50 c.c. with 20  $\mu$ g of hyaluronidase in the other. In the latter, induration was gone in five minutes, while the former lasted one hour. Following that, it was used in six other cases with the observation that it facilitated absorption and was even more effective when the plasma was diluted with saline in a 1:1 ratio. In one infant with severe diarrhea, a local pocket of boggy edematous tissue formed and absorption was delayed. Examination revealed a total serum protein of 4.7 per cent. As soon as plasma was given intravenously, the fluid absorbed and further clyses were also absorbed with-

out any trouble. This case suggested that marked alterations in intracellular structure, plus intercellular changes could hinder the absorption despite the hyaluronidase.

Its effect on the administration of subcutaneous or intramuscular blood was also studied in three cases. In a 1-year-old female infant with malnutrition and anemia, 100 c.c. were given with 20  $\mu$ g of hyaluronidase in each thigh. At a rate of 12 to 16 drops per minute, it was completed in three hours, with only slight evidence of swelling and erythema which was gone in two hours. In another case, on the first day blood was given diluted one and one-half times with saline, on the second day with equal parts of saline, and on the third day undiluted. The hemoglobin rose from 6.6 Gm. to 7.5 Gm. with the most noticeable improvement after the whole blood. In the third case, blood was diluted with equal parts of saline and the hemoglobin increased from 10.5 Gm. to 12 Gm. It appeared during the administration that when the blood was diluted, the hemoglobin did not rise much because the blood volume was probably increased and diluted by the saline; but with undiluted blood, the effect was more marked.

Its effect was also studied in two cases of hydrocephalus with the hope that intraventricular instillations would prevent progressive increase in the size of the skull. While the circumference did not increase during its administration, there was only a slight but not a very material decrease. One of the patients received 145  $\mu$ g in ten days and the other 900  $\mu$ g in sixty days. No ill effects were noted and this would tend to reaffirm the apparent wide range of safety of this drug.

#### SUMMARY AND CONCLUSION

1. Hyaluronidase was used subcutaneously in sixty cases, of which fifty were with electrolytes, seven with plasma, and three with blood.

2. It definitely facilitated absorption in all cases.

3. Its effect on intraventricular fluid in hydrocephalus was indefinite and requires further investigation, but the dosages used proved the drug's relative lack of toxicity.

4. Skin-testing only revealed a 2.1 per cent of sensitivity, with the percentage decreasing as more purified products were used. Furthermore, only one child had apparently acquired sensitivity to the product when rechecked, while seven allergies became nonsensitive after three months.

5. Conjunctival testing has failed to reveal any reaction to date but appears to be inferior to skin-testing for this product.

6. In view of its demonstrated harmlessness, and because of its apparent effectiveness, hyaluronidase should be a useful aid in the administration of fluids by clysis.

We have been greatly aided in this study by Dr. Morrison Levgarg and Dr. M. Price Meek, Pediatric Residents at the Metropolitan Hospital.

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## ASSOCIATED FACIAL AND INTRACRANIAL HEMANGIOMAS

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HORROCKS,<sup>1</sup> in 1883, reported the case of a 9-year-old mentally deficient boy who had a vascular nevus of the right side of the face, a network of vessels over the sclera, and tortuous retinal veins. Since birth the child had suffered seizures involving the left side of the body and had developed left-sided hemiplegia with contractures of the left arm. Horrocks postulated the presence of an angiomatous malformation of the pia mater on the right side as the cause of the convulsions. In 1897 Kaliseher<sup>2</sup> described a patient with a similar history and comparable physical findings. At autopsy an extensive venous angioma of the pia was found and the left hemisphere proved to be smaller than the right. Volland<sup>3</sup> later reported a patient exhibiting the same clinical picture in whom, in addition to a pial angioma, there was found calcification in the cerebral cortex. In 1921 Wissing<sup>4</sup> called attention to a singular shadow demonstrable by x-ray in the occipital region of an epileptic who had a vascular nevus of the face. The first published account of a similar finding was by Weber<sup>5</sup> in 1922. The x-ray shadow was believed to be due to calcification in the pial vessels until Krabbe,<sup>6</sup> in 1932, showed that the deposits in such cases were in the cortex, not in the pial angioma. His microscopic findings resembled those of Volland. Cushing<sup>7</sup> was the first to describe cases of this disorder in the American literature.

This association of facial and cerebral angiomas, with or without epilepsy, cortical calcification demonstrable by x-ray, and eye symptoms, has been given a variety of names: the Sturge-Weber or Sturge-Weber-Dimitri syndrome, Sturge's disease, Krabbe's disease, Kaliseher's disease, the Brushfield-Wyatt syndrome, neurocutaneous syndrome, encephalotrigeminal angiomatosis, nevoid amentia, and the cerebrocutaneous syndrome. In the literature available to us we have found 192 cases. This number does not include those reported as abortive type, in which either the facial angioma was not present or evidence of meningeal involvement was not shown.

### CASE REPORT

F. C., a 2-year-old white female child of Italian-American parentage, was referred to the Boston Floating Hospital because of convulsions. The family history is of interest in that two paternal consins have "birthmarks," one on the forehead, the other on the posterior neck. Two siblings are normal.

The child was born in a local hospital after a full-term pregnancy which was uneventful except for a great deal of vaginal bleeding. Delivery was aided by forceps after two to three hours of labor. At birth the infant appeared to be normal in all respects save that a port-wine nevus was present over the right

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side of the forehead. The neonatal period was uneventful. The child sat up at 6 months of age, stood and walked at 13 months, talked at 14 months. About one and one-half months before admission a moderate amount of bright red blood had appeared in her stools on a few occasions. She was said to be always very irritable and to cry a great deal without apparent cause.

At the age of 13 months there occurred a convulsion which lasted about one-half hour and was confined to the left side. At 19 months a second seizure occurred, similar to the first in character and duration. Before each episode, according to the family physician, there was evidence of an upper respiratory infection and a rise in temperature. Five days before admission she became more irritable than usual and developed a fever. While in the office of her pediatrician she vomited and had a left-sided convulsion which lasted nearly an hour. During the next few days she was very listless. On the day preceding admission her mother noted many episodes of "staring into space," during which the child's attention could not be gained. On the morning of admission there were several similar attacks. Between them she was apparently in possession of her faculties but showed little animation. Late in the morning she vomited, became stiff, and turned blue. One hour later, while in another hospital, a left-sided convulsion started and she was then brought to this hospital. Her father stated that each convulsion had begun with twitching on the left eye and the left corner of the mouth. The seizure then spread to the left hand and arm and then to the left leg. The head and eyes had always been turned to the left.

On admission her temperature was 100.4° F., pulse 92, respirations 30. She was in a continuous seizure which involved only the left side. There were twitching of the left lids and cheek and clonic movements of the left extremities. Three hours after its onset the convulsion was controlled with ether after all other methods had failed. Examination some time later revealed an attractive, well-developed child. The head was normal in size, symmetrical, and well shaped. There were no pulsations or bruits over the skull. A dusky rose, smooth, flat nevus extended from the margin of the upper lid on the right to the vertex and laterally to the extent of the eyebrow. It did not cross the midline and involved only a small portion of the nose. Its distribution was thus confined within the limit of the ophthalmic branch of the trigeminal nerve. The eyes were normal in size and did not protrude. The pupils were round, regular, and equal and reacted normally to stimuli. The sclera and conjunctiva were normal, as were extraocular movements. Fundoscopic examination showed the discs to be sharply outlined and there was no overgrowth, tortuosity, or dilatation of the retinal vessels. Vision apparently was normal. There was no angiomatous involvement of the nasal or buccal mucosa. The teeth were in good condition except for an enamel defect of an upper incisor. The lungs were clear. The heart was unremarkable except for a soft systolic murmur in the fourth left interspace near the sternum. Abdomen and external genitalia were normal. A rectal examination demonstrated no pathology. The extremities were of equal length and circumference. Muscle tone was normal. Tendon reflexes were three plus and equal. Plantars were flexor. Gait, station, and sensation were normal. The skin of the trunk and extremities was without blemish except for a small *café au lait* spot on the right lower abdomen.

*Laboratory Data.*—The urine was negative. The cellular constituents of the blood were within normal limits, as were the calcium, phosphorus, phosphatase, nonprotein nitrogen, and cholesterol. The cerebrospinal fluid four hours after cessation of the seizure was under normal pressure and was clear. Protein, sugar, and chlorides were normal in amount. A tuberculin test was negative. X-ray examination of the chest showed no abnormalities. X-ray examination

of the skull showed no abnormalities of the bony structure or signs of increased intracranial pressure. In the left side of the cerebellum was seen a 4 mm. rounded and sharply delineated area of calcification, the central portion of which was more radiolucent than the more peripheral portion. A pneumoencephalo-

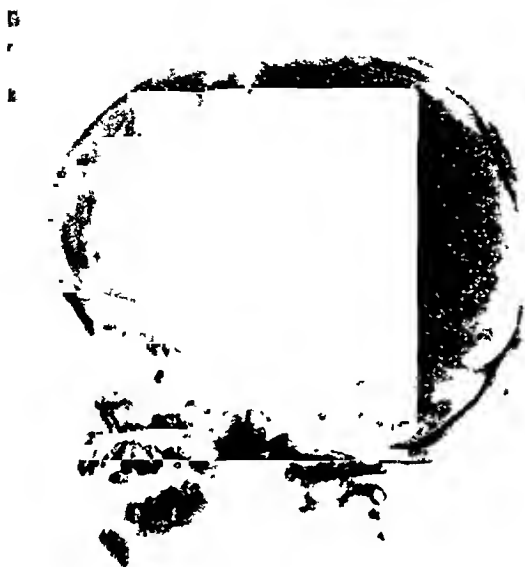


Fig. 1—Lateral view of skull showing calcification in left cerebellum

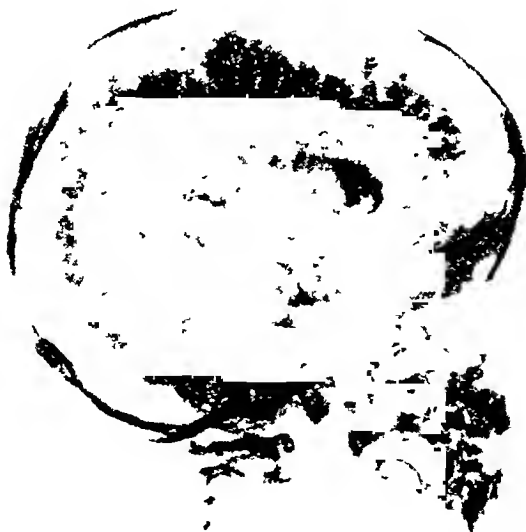


Fig. 2—Lateral view of pneumoencephalogram showing calcification in the left cerebellum and slight dilatation of the ventricles

gram was done following the introduction of 80 c.c. of air. The ventricular system and brain surface were well visualized. There was slight but definite dilatation of the entire ventricular system, including the fourth ventricle and the cisterna magna. There was no evidence of a filling defect or shift of the intracranial contents. From this study it was concluded that there was mild but definite deficiency of cerebral and cerebellar tissue probably associated with a small mass in the left cerebellum, possibly an hemangioma. An electroencephalogram showed definite focal slow wave activity occurring in the right hemisphere, most marked in the motor and occipital regions and suggesting localized pathology. Because of the earlier episode of melena, a barium enema and upper gastrointestinal series were done to demonstrate a possible angioma. These were negative. The child's I.Q. on the Revised Stanford-Binet test was 100.

The patient's hospital course was uneventful. She exhibited post-ictal somnolence for several hours and then was very irritable for a few days. Her disposition gradually improved, although she was prone to short temper tantrums on slight provocation. There were no further seizures.

For the following six months the child was followed by her pediatrician. Her health was excellent during the period and she received no medication. To her parents she appeared to be normal. She was returned to this hospital at the expiration of the term. At that time there was no change in the physical findings. X-ray examination of the skull showed the cerebellar calcification to be unchanged. An electroencephalogram was interpreted as showing a basically slow pattern, normal for age. Because of movements the record was unsatisfactory. A right carotid cerebral angiogram was done at the Children's Hospital. The films showed the internal carotid artery to be well filled and normally placed. The middle cerebral artery was well visualized and rose in normal fashion. The anterior cerebral artery was not satisfactorily visualized, apparently due to nonfilling, the cause of which was not clear. To the viewer it did not seem likely to presuppose an anterior cerebral thrombosis on this basis alone.

#### COMMENT

This case illustrates four of the five cardinal features of the condition: nevus over the trigeminal area, seizures of the Jacksonian type, intracerebral calcification, and psychic disturbance. Ocular abnormalities did not appear. The area of calcification was unusual in that it appeared in the cerebellum. Whether or not there are deposits in the cerebral cortex which are not dense enough to be demonstrable by x-ray examination, it is naturally impossible to say. It was expected that the cerebral angiogram would show evidence of an angioma over the right hemisphere but, except for the nonfilling of the anterior cerebral artery, the cause of which is speculative, the findings were normal. This does not indicate, however, that an angioma over the hemisphere is not present. It is believed that we are dealing here with one of a diffuse capillary type not shown by this technique.

#### CLINICAL AND LABORATORY FINDINGS

The condition has been discovered in all age groups, the first signs appearing in most cases, however, in early childhood. Boys are somewhat more frequently affected than girls. Heredity appears to play a part in some instances, although the evidence for this is slight. The nevus is usually of the flat, port-wine variety,



and is smooth, although it may be cavernous, rough, warty, or thickened and cause marked asymmetry of the facial structures. It is practically always within the distribution of one or more branches of the trigeminal nerve and in the great majority of cases is unilateral. The size varies. The whole trigeminal area may be involved or only a small portion of one or all divisions. Instead of a typical nevus there may be merely dilated or pulsating vessels. Except in rare cases the facial and cerebral angiomata are on the same side. In one of Oppenheim's<sup>8</sup> patients the nevus was on the left side of the face and the seizures involved the same side of the body, indicating that the cerebral pathology was probably on the opposite side. He offered three possible explanations for this: (1) reflex epilepsy, (2) spread of the angioma to the opposite side, and (3) failure of pyramidal crossing. In the case of Vincent cited by Weber<sup>5b</sup> contralateral angiomata were demonstrated at autopsy. In some cases other elements enter the make-up of the facial lesion. In the case reported by Greig,<sup>9</sup> for example, the type of telangiectasis seen in tuberose sclerosis was found. In two of the cases reported by Yakovlev and Guthrie,<sup>10</sup> polypi resembling those found in neurofibromatosis were associated with the nevus. The buccal and nasal mucosa may be involved, with epistaxis a prominent symptom. Other portions of the body surface are commonly affected, the side bearing the facial lesion as a rule most extensively. The lungs, liver, kidney, and intestines have shown associated hemangiomas. In our patient melena indicated the possibility of an intestinal lesion but this could not be demonstrated by barium study.

Convulsions occur in slightly more than 75 per cent of cases. They are usually Jacksonian but may be generalized, or they may be Jacksonian early, later becoming generalized. Petit mal-like episodes are not uncommon. The first seizure occurs in infancy in most cases. Subsequent convulsions may be suffered infrequently with long free periods or regularly at short intervals. There is nothing characteristic in the seizure picture. Status epilepticus may occur terminally. In many patients, as in ours, a rise in temperature accompanies and precedes the seizure. Hemiplegia or monoplegia with resulting atrophy and contractures is often seen, or there may be transient weakness of one or more of the extremities following a convulsive episode. Hemiplegia may occur without convulsions, becoming apparent shortly after birth or when ambulation is first attempted. Thrombosis or rupture of a vessel in the cortex is the usual explanation. The electroencephalograph has been employed in relatively few cases, the most common finding being a slow wave focus on the side affected by the nevus.

The intracranial calcification is demonstrable roentgenographically in about 50 per cent of cases of this disorder. It may be present without being visible, however, for in some instances autopsy or operation has demonstrated concretions after negative x-ray reports.<sup>11</sup> Usually it presents the aspect of sinuous, double contoured lines which seem to follow the outline of the cerebral convolutions. It may appear in the form of a single, sharply delineated shadow or as few or multiple flecks or granules. The occipital lobe is the most frequent area of election, but the frontal, temporal, and parietal lobes may be involved singly or in combination. Cerebellar localization is extremely rare and indicates an

associated angiomatous process in that area. The concretions appear on the same side as the facial nevus, although this did not hold true in our patient or in that of Wissing.<sup>12</sup> In only very few cases have serial x-rays been taken, so that it is impossible to state the speed of progression of the calcifying process. In one case reported by Anderson<sup>13</sup> there was a considerable increase in a period of three years. The x-ray often reveals the bony structure overlying the angioma to be thickened. The diploï may be widened. In some cases the frontal sinus on the affected side is larger than its opposite. Pneumoencephalograms have been performed in a number of cases, usually with results indicating cortical atrophy on the side involved in the angiomatous process.

Lumbar puncture, as would be expected, is productive of normal findings except for rare instances of elevated pressure.

Ocular abnormalities are found in some 70 per cent of these patients. As a rule the affection is unilateral, occurring on the same side as the nevus. There may be angiomatous changes in the sclera, conjunctiva, or retina. Buphthalmos or glaucoma is common, with varying degrees of impairment of vision. Homonymous hemianopsia, retinal pigmentation, iris atrophy, heterochromia, optic atrophy, pupillary abnormalities, coloboma, strabismus, disturbances of the reflex mechanisms, and nystagmus may be found singly or in various combinations.

Psychic disturbances are reported in approximately 50 per cent of cases, ranging in severity from poor memory, inability to concentrate, or behavior disorders, to idiocy and dementia. In many cases the mental defect seems to depend upon the frequency of the convulsions, deterioration resulting from repeated severe seizures. In others the defect is possibly primary.

Endocrine disturbances have been mentioned in connection with the syndrome. Safar's<sup>14</sup> patient was a 28-year-old man with female distribution of hair, sparse beard, and hypoplasia of one testicle; that of Fedoroff and Bogorad,<sup>15</sup> a 23-year-old woman with no menses after the age of sixteen, little hair on mons or in axilla, and undeveloped breasts. The patient reported by Weber<sup>5</sup> was a 22-year-old woman who was obese, had infantile sex characteristics, had no pubic or axillary hair, and had not menstruated. In a number of cases in young boys adiposogenital dystrophy is described, but in no case is evidence offered that the patient's appearance was not due merely to juvenile obesity.

#### PATHOLOGY

Pathologic findings at operation or autopsy have been fairly uniform. When the skull is opened the dura is usually found to be thickened and unusually vascular on the affected side. The pia is the site of an angioma of varying size and character or the vessels are merely increased somewhat in number or widened. The occipital area is most markedly affected, although the temporal, parietal, and frontal areas may be involved. The cerebellum is rarely affected. Beneath the vascular defect the cortex is shrunken. The gyri are flattened, small, and feel hard to the touch. On section, if calcification is present, it appears as a ribbon running through the cortex or as chunks separated by gliosed tissue. If not seen macroscopically, the cut surface may yet feel gritty. Owing to

cortical atrophy the ventricle on the affected side is dilated. There may be angiomas found in the brain substance. Areas of hemorrhage and thrombosis may be apparent. Microscopically the pial angioma is made up of endothelial-lined blood spaces. The connective tissue is small in amount. Calcification in the vessel walls is sometimes found but is not a prominent feature. The cortex beneath is thin, with diminished or absent nerve cells and increase in gliosis. Calcification is noted in all the layers of the cortex, being most marked in the second and third layers, where the normal tissue may be completely replaced. The white substance is rarely affected. The precipitate is seen within and surrounding the walls of the precapillaries and capillaries and also free in the tissue. It appears in the form of isolated beads on the vessel walls or as mulberry-like clusters completely encircling them. The lumens may be entirely obliterated, with diminution of the vascular bed. All stages of vessel involvement may be seen in a section. The concretions which lie free in the tissue are seen as irregular granules of varying shape. They seem to bear no relation to the blood vessels. All calcified areas are surrounded by glial tissue.

Microscopic examination of the affected eye often shows angiomatous involvement of the iris, and particularly of the choroid. Adhesions may be found in the angle of the anterior chamber.

#### PATHOGENESIS

There is general agreement that the angiomatosis is a defect of mesodermal origin and that the anomaly is a result of a disturbance in early fetal life. The association of the trigeminal nevus with angioma of the choroid, retina, and meninges is accounted for by the fact that in early fetal life the areas are in close proximity and their vascular systems arise from a common capillary sheet. As the meninges and skull develop this common vascular bed splits up into three layers of superficial, dural, and pial vessels, for the skin and the meninges respectively.<sup>16</sup> With continued growth of the fetus these vascular layers and the structures they supply become more and more widely separated until they assume their definitive positions.

In regard to the cortical changes, two schools of thought exist. The one holds that there is an ectodermal defect coordinated with the mesodermal dysplasia, the other that the atrophy, gliosis, and calcification are secondary to the pial anomaly. Yakovlev and Guthrie<sup>10</sup> believe that the gliosis is a primary process and takes an active part in the abnormality. They believe the vascular derangement to be only a more conspicuous part of a malformation which affects the cerebrum as a whole and that a developmental factor is more important in the causation of the convulsive phenomena than the vascular lesion. Krabbe,<sup>6</sup> Nussey and Miller,<sup>17</sup> and Scheinker,<sup>18</sup> among others, also believe the cortical defect to be primary and independent of the pial vessel abnormality. Numerous authors link the condition with neurofibromatosis (von Recklinghausen), hemangioblastoma of the retina and cerebellum (von Hippel-Lindau) and tubercose sclerosis, grouping the four conditions under the term phakomatosis and professing to see in them common elements of ectodermal and mesodermal dysplasia.<sup>10, 19, 20</sup>

Alexander and Woodhall,<sup>21</sup> Bergstrand,<sup>22</sup> Peters,<sup>23</sup> Lichtenstein and Rosenberg,<sup>24</sup> and Green<sup>25</sup> are among those who believe that the cortex is developmentally normal and that the pial anomaly is responsible for the calcification and other cortical changes and, thus, for the neurologic manifestations. Alexander and Woodhall, and Lichtenstein and Rosenberg postulate that the calcification arises as a result of incomplete interference with the blood supply of the affected areas. Disturbances of circulation within the abnormal vascular channels leads to a lowered metabolism of the underlying cortex, vascular damage, and necrosis, with subsequent influx of calcium into the area. The incompleteness of interference with the blood supply is important. Were it complete there would be no calcification because there would be no means for its deposition. Green,<sup>25</sup> in attempting to explain the reason why the second and third layers of the cortex are most affected in the calcification process, points out that this area normally contains more capillaries than the superficial and deep layers and, also, that this is the junction area of the central and peripheral blood supply of the brain. It is not inconceivable that such an area might suffer most in the presence of vascular anomalies.

Various explanations have been given for the production of buphthalmos and glaucoma: stasis in angiomatous vessels with consequent increase in intraocular pressure,<sup>26</sup> vascular changes in the ciliary body and choroid, either preventing development of the canal of Schlemm or causing blockage of the filtration angle<sup>27</sup>; impairment of sympathetic innervation<sup>28-30</sup>; increased transudation from the increased vascular tissue and diminished outflow of intraocular fluid.<sup>31</sup> Ballantyne<sup>32</sup> suggests that in some cases the angioma may be sufficiently developed in antenatal life to establish buphthalmos, while in others the growth is delayed to adult life with the production of secondary or simple glaucoma.

#### DISCUSSION

The clinical and pathologic findings seem to indicate that we are dealing with a purely mesodermal primary defect, an angiomatous malformation, at least in the majority of cases, in this syndrome. Were a primary ectodermal dysplasia the rule, one would expect symptoms of disturbed mentation to be more constant in incidence and severity. Instead, we find roughly 50 per cent of patients with no psychic difficulties and in many of the remainder a progression of the mental defect only as severe seizures are often repeated. There seems to be no necessity for postulating an accompanying ectodermal maldevelopment to account for the cortical changes and the neurologic manifestations. A pial angioma, like a subdural hematoma, occupies space normally provided for other structures in the intracranial economy. If large enough, there is pressure on the cortex. Added to this is the factor of circulatory derangement. Circulation within intracranial angiomas is slowed.<sup>25, 33</sup> As a result of this relative stasis the process of calcification, gliosis, and further atrophy as outlined by Woodhall and Alexander, and Lichtenstein and Rosenberg take place.

#### DIAGNOSIS

A strong presumptive diagnosis of an intracranial angioma can be made in a patient with a facial nevus who has convulsive seizures or exhibits signs of a

cerebral vascular accident. It is confirmed by the presence of intracerebral calcification demonstrated by x-ray, by angiography, or by surgical exploration.

Inasmuch as treatment, whether radiation or surgery, depends for its greatest efficacy on institution before irreversible cortical changes have taken place, an early diagnosis is important. Any child with a trigeminal nevus should be studied to rule out, so far as possible, an accompanying meningeal or cortical lesion. If the diagnosis is not made before the appearance of seizures or hemiplegia or before calcification can be seen by x-ray, extremely valuable time may have been lost. In the presence of such a condition, it is important at least to secure x-ray examination of the skull, an electroencephalographic study, and, perhaps, a pneumoencephalogram. Angiography might be advisable if facilities are available. That this latter step, in the absence of signs and symptoms, is in some cases justified, is attested to by the case of a child who was apparently normal in all respects except for a trigeminal nevus but who was proved to have an intracranial angioma by carotid angiography.<sup>34</sup>

#### SUMMARY AND CONCLUSIONS

A case of associated facial and intracranial angioma is presented, together with a brief review of the clinical and laboratory findings.

The pathology is described and an exposition given of the theories advanced as to the pathogenesis of the condition.

The defect is probably primarily mesodermal in origin, with cortical changes secondary to pressure and interference with circulation in the area lying beneath the angioma. Ocular and cerebral involvement in cases of facial nevus may depend upon the time of initiation of the mesodermal defect. Before cleavage of the primitive vascular sheet, all three structures may show vessel abnormalities; afterward, one or a combination of two.

It is important that the diagnosis be made before signs of intracranial pathology appear. To this end, electroencephalography and contrast and air studies should be considered in cases of children who have trigeminal nevi.

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## CYANOSIS IN PREMATURE INFANTS DUE TO ANILINE DYE INTOXICATION

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THE majority of cases of aniline dye poisoning among infants in the past have been due to cutaneous absorption from the buttock area. Rayner<sup>1</sup> first reported seventeen such cases from London in 1886. It was not until thirty-four years later that a second report appeared.<sup>2</sup> A review of all available literature at this time reveals a total of sixty-three such cases recorded in seven reports.<sup>1-7</sup> In an unpublished study, Altman<sup>8</sup> observed ten cases in newborn infants in 1932. In addition, Stevens<sup>9</sup> reported two cases which were due to inhalation of a disinfectant containing nitrobenzene; Zeligs' series<sup>4</sup> contained one with a similar etiology.

Most of these cases have been among full-term newborn infants. There was a total of five deaths among the sixty-three cases.<sup>6, 7</sup> Four fatalities occurred in one outbreak,<sup>6</sup> and the patients all expired with bronchopneumonia (one associated with intracranial hemorrhage) about three weeks after the poisoning. Of the five fatalities, four were in premature infants.

This report is based upon a study of nine premature infants who developed aniline intoxication traced to the dye used in stamping diapers. The purposes of the report are to call attention to this important cause of cyanosis, to stress the fact that it can be prevented by simple measures, and to show that it can be treated satisfactorily even in premature infants if recognized early. It is important that knowledge of the means of preventing its occurrence be spread as widely as possible.

Aniline,  $C_6H_5NH_2$ , is a colorless, oily, highly refracting liquid having a characteristic aromatic odor and a burning taste. It is derived from the reduction of nitrobenzene. It turns yellow to brown when exposed to air. Although only slightly soluble in water (1:31), aniline mixes readily with alcohol, ether, benzene, or chloroform. It is used mainly to synthesize aniline dyes and in the manufacture of rubber.<sup>10</sup> Hospitals and day nurseries often use aniline dyes to stamp the name of the institution on diapers and other linen. Intoxication may occur from the inhalation of aniline or nitrobenzene vapors, by cutaneous absorption, or by ingestion. The most evident sign of the intoxication is a peculiar grayish cyanosis. Dulstin and associates<sup>11</sup> attributed this to a pigment formed in the subcutaneous tissue by aniline. The blood itself becomes dark and on exposure to air does not change to its usually bright red color. Spectroscopic examination of the blood reveals the presence of methemoglobin.

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The actual mechanism of formation of methemoglobinemia by aniline is a matter of dispute. When aniline is mixed directly with blood, methemoglobin formation is very slow, and in sixteen hours only one-half molecule of methemoglobin is formed per molecule of aniline. This has been taken to suggest that aniline can change hemoglobin to methemoglobin only after the aniline has been changed to a more active oxidizing agent. It has been postulated that paraminophenol or some oxidation product such as hydroxyphenylhydroxylamine is the substance responsible for the alteration in hemoglobin. There is also a possibility that some highly pigmented oxidation product of paraminophenol may be present in the blood and tissues and in itself may enhance the bluish color of the skin. Methemoglobin is formed from hemoglobin by the action of an oxidizing agent, and it is readily turned back to hemoglobin by an equivalent amount of reducing agent. Presumably the ferrous ion of hemoglobin is changed to the ferric ion in methemoglobin. Since less hemoglobin is then available for oxygen transport, a "functional anemia" develops.<sup>12</sup> Darling and Roughton<sup>13</sup> point out that the tissues of the body are liable to anoxemia in methemoglobinemia, not only from the loss of oxygen-carrying capacity of the blood but also because, as the amount of methemoglobin in the blood increases, the blood has increasing difficulty in releasing to the tissues whatever oxygen it contains.

In the treatment of methemoglobinemia of various etiology in adults and children, oxygen inhalation, blood transfusions, methylene blue, and ascorbic acid have been the principle measures tried. In the treatment of aniline dye poisoning in infancy all these measures except ascorbic acid have been used in the past. There has been considerable disagreement as to the value of methylene blue in combating this disorder. In high concentrations it converts the ferrous ion of reduced hemoglobin to the ferric form and methemoglobin, whereas in low concentrations it apparently reverses this process.<sup>14</sup> Wendel<sup>14</sup> found that "following intravenous injection of small amounts of methylene blue, methemoglobin rapidly disappears from the blood and is replaced by an equivalent amount of hemoglobin." Although oxygen and blood transfusions have been used empirically as supportive therapy, oxygen is of doubtful value; and Wallace<sup>15</sup> reported one case of methemoglobinemia due to bismuth subnitrate in which transfusion of washed red blood cells resulted in an increase of the cyanosis. Lian and associates,<sup>16</sup> in France in 1939, were probably first to use ascorbic acid in the treatment of familial methemoglobinemia. Ascorbic acid was subsequently used successfully by Deeny and associates<sup>17</sup> in England in 1943, Graybiel and co-workers<sup>18</sup> in the United States in 1945, and Carnrick and associates<sup>19</sup> in 1946. Because of the marked reducing properties of ascorbic acid, the absence of untoward reactions, and the experience of these investigators with it in idiopathic congenital methemoglobinemia, we considered it advisable to try it in our cases of aniline dye poisoning.<sup>2</sup>

#### REVIEW OF CASES

There were thirty premature infants in the premature station on November 10, 1946. That morning it was noted that six of these infants suddenly became

\*Since this study was made, a case report has appeared in which ascorbic acid was used successfully in the treatment of methemoglobinemia due to nitrates in drinking water.<sup>20</sup>



ill. They had a grayish, cyanotic appearance and marked apathy. Subsequently, it was noted that three more infants in the station developed a similar but milder degree of cyanosis and apathy. The age of these nine patients ranged from 3 to 64 days (average 19 days), and the weights ranged from 1,000 to 2,015 Gm. (average 1,272 Gm.).

For a few days prior to this outbreak, a faint odor which was not impressive at the time but which on recollection seemed somewhat peculiar (resembling the odor of shoe polish) had been noted in the premature station. Subsequent investigation revealed that it had developed following an emergency requisition of a large number of diapers from the linen room. Through some delay in the routine supply, there developed a sudden urgent demand for clean diapers in the station. In an effort to comply immediately the laundry sent diapers which, through an oversight, had not been boiled after stamping. The dye used to stamp the diapers was composed of nigrosin for color and a mixture of aniline oil and oil of mirbane (nitrobenzene) as solvent. Some of the diapers were used in contact with the buttocks and others were placed around the infants' necks during their feeding periods. Furthermore, the infants were kept in the confined air space of an incubator, in which the dye may have volatilized. Therefore, both inhalation and cutaneous absorption were possible avenues for entrance of the intoxicant.

#### SIGNS OF INTOXICATION

All nine infants had a grayish cyanosis (six severe); four of the nine were markedly apathetic; six vomited; and five had various degrees of anorexia. All of these infants showed their first sign of intoxication within a period of forty-eight hours. (During this same period another infant became apathetic and vomited but was not cyanotic. It might be that these signs were due to aniline intoxication because of the simultaneous poisoning of the others and because the symptoms disappeared with the removal of the intoxicant at the same time as did those of the other patients. Because of the absence of cyanosis, however, the case of this infant is not included in the group of nine.) Unfortunately, it was not practical at the time to examine the blood spectroscopically for methemoglobin.

#### COURSE

All of the infants recovered. Five of the nine developed mild to severe bronchopneumonia between the second and fourth weeks following the poisoning. On the other hand, none of the other twenty-one infants who were in the premature station at the same time developed pneumonia.

#### THERAPY

Three of the premature infants who had the most marked signs and symptoms were given whole blood transfusions, oxygen inhalation, methylene blue, and ascorbic acid. Methylene blue was given intravenously once to each infant (0.1 c.c. of a one per cent solution was given in 5 c.c. of saline, a total dose of 1.0 mg.). Ascorbic acid was given in doses of 100 mg. orally once to one of the three and twice to the other two. Three equally ill infants were each given

ascorbic acid, 100 mg. orally once and no transfusion, methylene blue, or oxygen. In all six cases there was rapid improvement of symptoms. The remaining three cases were relatively mild and the patients were not treated with any of these measures. Recovery in these also was prompt with removal of the dye.

The therapeutic effect of ascorbic acid is difficult to evaluate since improvement began rapidly in all cases following removal of the offending dye. There is suggestive evidence that it may have prevented the signs of intoxication in the other infants. Of the nine infants who developed intoxication, eight had received no ascorbic acid in their diet previously, and one (whose symptoms were very mild) had received 25 mg. of ascorbic acid daily for two months. On the other hand, among the twenty in the station who did not develop the intoxication (excluding one questionable case noted above), ten had received 25 mg. of ascorbic acid daily for one to eight weeks, one had received 100 mg. of ascorbic acid daily for one week, and five had received 30 to 90 c.c. of fresh orange juice daily for seven to ten days. Two of the twenty did not receive ascorbic acid, and two others were not exposed to the dye because they died from other causes on the day of admission.

#### DISCUSSION

Aniline dye poisoning due to cutaneous absorption or inhalation is a condition which must be considered in the differential diagnosis of cyanosis and apathy in infants. Perhaps bronchopneumonia is a delayed complication which is not clinically apparent until several weeks after the intoxication. It was present in five of the nine cases in this series. There were no deaths in this group, but of the five reported deaths, four were in prematures who expired with bronchopneumonia about three weeks after the intoxication. With early recognition, removal of the offending chemical, and prompt therapy, the prognosis of this intoxication is good even in premature infants.

In order to prevent the occurrence of aniline intoxication it is of the utmost importance that all diapers be boiled *after* they are stamped. If followed by thorough drying, this would eliminate the possibility of such intoxication. Ideally, a dye should be used which is nontoxic to the human body. Unfortunately dyes made of vegetable pigments, charcoal, or silver nitrate lack the necessary permanence and with them also washing is advisable after stamping to avoid objectionable odors. In addition, the necessity of marking each diaper individually by hand when these dyes are used adds to the expense. The use of name tapes or colored threads is also relatively expensive. Until a fool-proof method of identifying diapers is found, the best means of prevention would seem to be through a widespread educational effort warning against the danger and urging the boiling and thorough drying of the diapers *after* they have been stamped.

#### SUMMARY

Since 1886, there have been seven reports of aniline dye poisoning among newly born infants involving sixty-three patients. In addition, there was an unreported outbreak involving ten infants, and it is quite likely that there have

been many more either unrecognized or unreported.<sup>21</sup> Among these cases, there were five deaths, four of these being premature infants who died with bronchopneumonia three weeks after the poisoning.

This report is based upon a study of nine premature infants who developed aniline dye intoxication traced to freshly stamped diapers. They developed the characteristic grayish cyanosis, and five developed bronchopneumonia between the second and fourth weeks after the intoxication. There were no deaths.

The pathogenesis and treatment are discussed. Early recognition of the condition and removal of the offending chemical are essential. Ascorbic acid warrants further trial as a therapeutic measure.

The importance of and methods for prevention should be made common knowledge; laundry personnel and all other individuals concerned should be impressed with the importance of withholding stamped diapers until *after* they have been boiled.

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# STUDIES ON ANTIBIOTICS IN THE CEREBROSPINAL FLUID

## I. THE INHIBITORY EFFECT OF NORMAL CEREBROSPINAL FLUID ON THE ANTIBACTERIAL ACTION OF STREPTOMYCIN

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### INTRODUCTION

RECENT *in vitro* studies by Tucker<sup>1</sup> have shown that normal cerebrospinal fluid has an inhibitory effect on the antibacterial action of penicillin. It has also been demonstrated that human serum exerts a similar inhibitory action on both streptomycin<sup>2</sup> and penicillin.<sup>3</sup> A protein-binding mechanism<sup>4</sup> was shown to be involved in the inhibitory effect of human serum on penicillin. This is in contrast to the findings of Tucker, which suggest that penicillin is actually destroyed by cerebrospinal fluid.

In view of these facts, the question arises whether the cerebrospinal fluid exerts a similar inhibitory action on streptomycin. It is the purpose of this paper to present data designed to answer this question.<sup>5</sup>

Very little is known about the influence of cerebrospinal fluid on antibiotic agents. Some of the problems in addition to the above which deserve clarification are: (1) the effect of cerebrospinal fluid from patients with meningitis on the antibacterial action of streptomycin and penicillin; (2) the effect of cerebrospinal fluid from patients with febrile illnesses other than meningitis on streptomycin and penicillin; (3) the mechanism of the inhibitory action of normal cerebrospinal fluid on streptomycin; and (4) further observations on cerebrospinal fluid levels of streptomycin and penicillin after parenteral administration in patients with damaged and undamaged meninges. Studies on these problems are to be reported later, and will have a bearing on the controversial subject of intrathecal administration of antibiotics in the treatment of meningitis.

### METHODS AND MATERIALS

Cerebrospinal fluid was obtained from seventeen patients admitted to the Children's Hospital. Most of these were brought into the hospital for elective surgery and none showed any evidence of meningeal pathology. All of the cerebrospinal fluid specimens were water-clear and none were contaminated with blood. The temperature of each patient was normal.

Bio-assay determinations for streptomycin were done by the method of Price, Nielsen, and Weleh.<sup>5</sup> This method utilizes the inhibitory effect of streptomycin in serial dilutions on the growth of *Bacillus circulans*.† Standards were

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\*Streptomycin Calcium Chloride Complex was used in this study.

†A standardized strain of *B. circulans* was obtained from the Food and Drug Administration Division of The Federal Security Agency, Washington, D. C.

prepared for each determination. Thus we were able to demonstrate the inhibitory effect of varying but known quantities of streptomycin on a constant dilution of the organism in broth. To set up these standards, ten tubes were arranged in series. One milliliter of nutrient broth was added to each of the tubes except the first. Ten micrograms of streptomycin in one milliliter of normal saline was placed in both the first and the second tubes. Beginning with the second tube, serial dilutions of streptomycin were extended through the ninth tube by transferring one milliliter of fluid to each succeeding tube. Therefore, the first tube contained 10  $\mu\text{g}$  of streptomycin, the second 5  $\mu\text{g}$ , and the third 2.5  $\mu\text{g}$ , ending with 0.03  $\mu\text{g}$  in the ninth tube. One-half milliliter of saline was placed in each of the ten tubes. This was necessary in order that comparable volumes would be present in the standard and the cerebrospinal fluid series. Lastly, one and one-half milliliters of 1:100 broth culture of *B. circulans* were added to each of the ten tubes after the dilutions were made. The tenth tube was the control tube and tested the viability of the organism, since it contained no streptomycin.

For testing the inhibitory effect of cerebrospinal fluid, three groups of ten tubes each were arranged in series. One milliliter of nutrient broth was placed in the second through the tenth tube. However, in contrast to the standard determinations, 100  $\mu\text{g}$  of streptomycin were pipetted into both the first and second tubes. Then, beginning with the second tube, the serial dilutions were made through the tenth tube. Thus the first tube contained 100  $\mu\text{g}$  of streptomycin, the second 50  $\mu\text{g}$ , and the third 25  $\mu\text{g}$ , ending with 0.18  $\mu\text{g}$  in the tenth tube. By starting with 100  $\mu\text{g}$  of streptomycin in the first tube, it was possible to test a wider range of inhibition and include the range of streptomycin concentrations in the standard series. The same quantity of the organism used in the standards was added to each tube. To one series 0.5 ml. of cerebrospinal fluid was added to each tube, to a second series 0.25 ml., and to a third series 0.1 ml. was added to each tube. Therefore, we were able to ascertain the effect of varying amounts of the same cerebrospinal fluid on the antibacterial action of streptomycin. The cerebrospinal fluid added to the tubes of the second and third series was diluted with a quantity of normal saline necessary to keep the volume and, therefore, the streptomycin concentration, constant in the corresponding tubes of each series.

The last tube in which growth of *B. circulans* was completely absent indicated the amount of streptomycin necessary to inhibit growth of the organism. These results were expressed as micrograms per milliliter, as outlined by Price, Nielsen, and Welch<sup>5</sup> in their original bio-assay method. It must be pointed out that the final volume in our experiments was 3 ml., whereas 2.5 ml. volumes were used by the aforementioned investigators. This variation becomes insignificant in the interpretation of our results, since, as stated previously, comparable dilutions were present in the standard and in the cerebrospinal fluid series.

#### RESULTS

Reference to Table I demonstrates the quantity of streptomycin necessary to inhibit the growth of *B. circulans* with and without cerebrospinal fluid.

TABLE I. THE RESULTS DEMONSTRATING THE INHIBITORY EFFECT OF VARYING QUANTITIES OF NORMAL CEREBROSPINAL FLUID ON STREPTOMYCIN USING *B. CIRCULANS* AS THE TEST ORGANISM\*

PATIENT	AGE	STREPTOMYCIN NECESSARY TO INHIBIT GROWTH ( $\mu\text{G/ML.}$ )			
		STANDARD	MILLILITER CEREBROSPINAL FLUID ADDED		
			0.5	0.25	0.1
1. J.S.	8 mo.	0.6	1.5	--	--
2. A.R.	3 yr.	0.2	1.5	--	--
3. P.H.	8 yr.	0.3	0.7	--	--
4. L.S.	2 yr.	0.6	6.2	6.2	--
5. B.J.P.	7 yr.	0.6	6.2	6.2	--
6. I.M.P.	9 yr.	0.6	3.1	3.1	--
7. A.N.	8 yr.	0.3	6.2	6.2	0.3
8. M.E.	10 yr.	0.3	3.1	3.1	0.3
9. J.M.	10 yr.	0.3	3.1	1.5	0.7
10. R.R.	11 yr.	0.3	3.1	3.1	0.7
11. G.Wi.	7 yr.	0.3	3.1	3.1	0.7
12. M.A.B.	4 yr.	0.3	3.1	3.1	0.3
13. G.Wr.	6 yr.	0.3	3.1	3.1	3.1
14. M.P.	6 yr.	0.3	3.1	1.5	0.7
15. M.B.	12 yr.	0.3	1.5	1.5	0.7
16. H.S.	15 mo.	0.1	1.5	1.5	0.7
17. E.M.O.	9 yr.	0.3	3.1	3.1	1.5

\*Experiments were not conducted where data are absent.

In the standards the organism was inhibited by  $0.3 \mu\text{g}$  per milliliter in the majority of the instances. The range was from  $0.1 \mu\text{g}$  per milliliter in Patient 3, to  $0.6 \mu\text{g}$  per milliliter in Patients 1, 4, 5, and 6.

In the presence of  $0.5 \text{ ml.}$  of normal cerebrospinal fluid, the quantity of streptomycin necessary to inhibit the organism in the majority of instances was  $3.1 \mu\text{g}$  per milliliter, and ranged from  $1.7 \mu\text{g}$  per milliliter in Patient 3 to  $6.2 \mu\text{g}$  per milliliter in Patients 4, 5, and 7. When  $0.25 \text{ ml.}$  of normal cerebrospinal fluid was added, the quantity of streptomycin necessary to inhibit the organism was  $3.1 \mu\text{g}$  per milliliter in seven of fourteen patients, and ranged from  $1.5 \mu\text{g}$  per milliliter in Patients 9, 14, 15, and 16 to  $6.2 \mu\text{g}$  per milliliter in Patients 4, 5, and 7. The quantity of streptomycin required to inhibit growth of *B. circulans* in the presence of  $0.1 \text{ ml.}$  of normal cerebrospinal fluid was  $0.7 \mu\text{g}$  per milliliter in the majority of the determinations; the range under these conditions was  $0.3 \mu\text{g}$  per milliliter in Patients 7, 8, and 12, to  $3.1 \mu\text{g}$  per milliliter in Patient 13.

An effect comparable to that of  $0.5 \text{ ml.}$  of normal cerebrospinal fluid was exerted by  $0.25 \text{ ml.}$  of cerebrospinal fluid on streptomycin in Patients 4 through 8, 10 through 13, and 15 through 17. However, in Patients 9 and 14 there was a decreased effect as compared with  $0.5 \text{ ml.}$  When  $0.1 \text{ ml.}$  of cerebrospinal fluid was added, a smaller but definite inhibitory effect on streptomycin was demonstrated in eight of eleven patients. This effect was not demonstrated in the remaining three patients. Such variations in any one series would be expected within the limits of accuracy of bio-assay determinations.

## DISCUSSION

From the results of this study we were able to demonstrate a definite inhibitory action of normal cerebrospinal fluid on the antibacterial action of streptomycin. In the presence of  $0.5 \text{ ml.}$  of cerebrospinal fluid, it was demonstrated

that approximately ten times as much streptomycin was necessary to inhibit the growth of *B. circulans* as in the standard. The average quantity of streptomycin necessary to inhibit growth of *B. circulans* in the presence of 0.25 ml. of cerebrospinal fluid was also approximately ten times that in the standard. In the presence of 0.1 ml. of cerebrospinal fluid, approximately two and one-half times the quantity of streptomycin was necessary to inhibit the organism.

Analysis of these data suggests that there is a quantitative relationship between the amount of cerebrospinal fluid and its inhibitory action on streptomycin, since considerably greater inhibition was demonstrable in the presence of 0.5 ml. of cerebrospinal fluid than in the presence of 0.1 ml.

It is interesting that with low concentrations of cerebrospinal fluid, a definite inhibitory effect was present. These data suggest that the inhibitory mechanism, whatever its nature may be, is a relatively potent one. These facts further suggest that although some streptomycin may reach the cerebrospinal fluid after parenteral administration, it may not be detectable by present bio-assay methods. The cerebrospinal fluid may inhibit or may destroy the streptomycin in low concentration. The mechanism of this action of normal cerebrospinal fluid cannot be explained at this time.

#### SUMMARY AND CONCLUSIONS

1. Specimens of cerebrospinal fluid from seventeen patients with no evidence of meningeal pathology were tested for their inhibitory effect on the antibacterial action of streptomycin.

2. The antibacterial action of streptomycin is definitely inhibited in the presence of normal cerebrospinal fluid.

3. There is a suggestion of a quantitative relationship between the amount of cerebrospinal fluid and its effect on the antibacterial action of streptomycin.

4. This inhibitory action of normal cerebrospinal fluid on streptomycin may prevent the detection of antibiotics in the cerebrospinal fluid by present methods of bio-assay.

Grateful acknowledgment is made to Dr. James N. Etteldorf and Dr. James G. Hughes for advice and suggestions during the course of this work and in the preparation of this paper.

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## CONGENITAL SARCOMA

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IN 1940, Wells<sup>1</sup> published an exhaustive review of malignant congenital tumors in which he subjected all cases reported up to that time to careful scrutiny. Because of insufficient data, 150 cases were classified by him as possible, twenty cases as probable, congenital sarcomas. There remained a group of thirty cases, including one published by Paek and Anglem,<sup>2</sup> which was accepted as certain. If one omits the rather frequent congenital neuroblastoma of the retina, these thirty cases represent more than one-half of all accepted congenital malignant tumors. Since 1940, no additional cases have been listed in the *Quarterly Cumulative Index Medicus*. Even assuming that a number of such tumors have been sporadically observed but remained unreported, one must consider congenital sarcoma an exceedingly rare neoplasm.

It is to be expected, therefore, that a newborn child with such a tumor presents an almost unique problem to the attending physician who most likely has never seen a similar case before. What is the degree of malignancy of such a tumor? What is the outlook for the patient? How should the condition be treated and especially can mutilating operations in an infant be avoided? Any additional experience with such lesions should be interesting so that the following case of congenital sarcoma of the foot is reported.

### CASE REPORT

A white male infant (Admission No. 48,819) was born on Sept. 25, 1947, in this hospital. Delivery was at term and normal. On October 3, one week after delivery, a lump the size of a split hazelnut was noted on the back of the right foot. The family physician thought it was a ganglion and attempted to crush it, without success. Instead, the mass became rapidly larger and the baby was referred to this hospital for biopsy on November 6. An ill-defined firm mass of slightly bluish color was present on the dorsum of the right foot. It measured about 2 cm. in diameter. It was incised and diffuse pinkish-grayish glistening tissue was encountered which involved the subcutis and the dorsal tendons. Removal was impossible and a biopsy was taken. It showed a diffusely growing tumor composed of medium-sized ovoid cells with hyperchromic nuclei. Atypical nuclei and mitoses were seen. Many lymphocytes and plasma cells and a considerable amount of brownish pigment, identified as hemosiderin, were present. A diagnosis of spindle-cell sarcoma was made.

Amputation was advised, but because of the gravity of such a decision, consultation was arranged with the Memorial Hospital in New York City. The child was seen there on November 24. The diagnosis of sarcoma was confirmed and amputation of the leg recommended—exarticulation in the hip if the inguinal lymph nodes contained tumor.



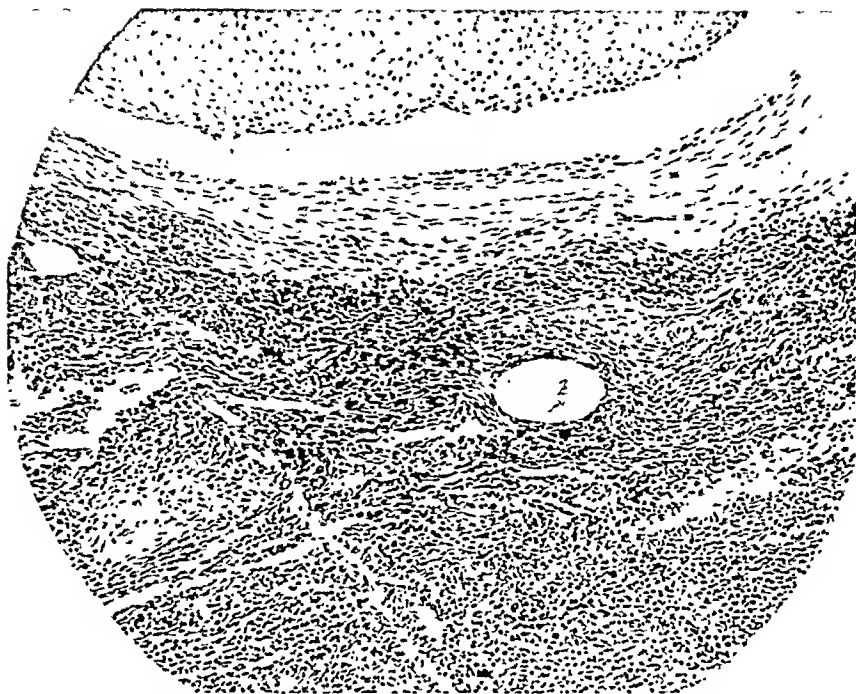


Fig. 1.—The tendon is seen on top. The tumor is in intimate relation to the tendon sheath.

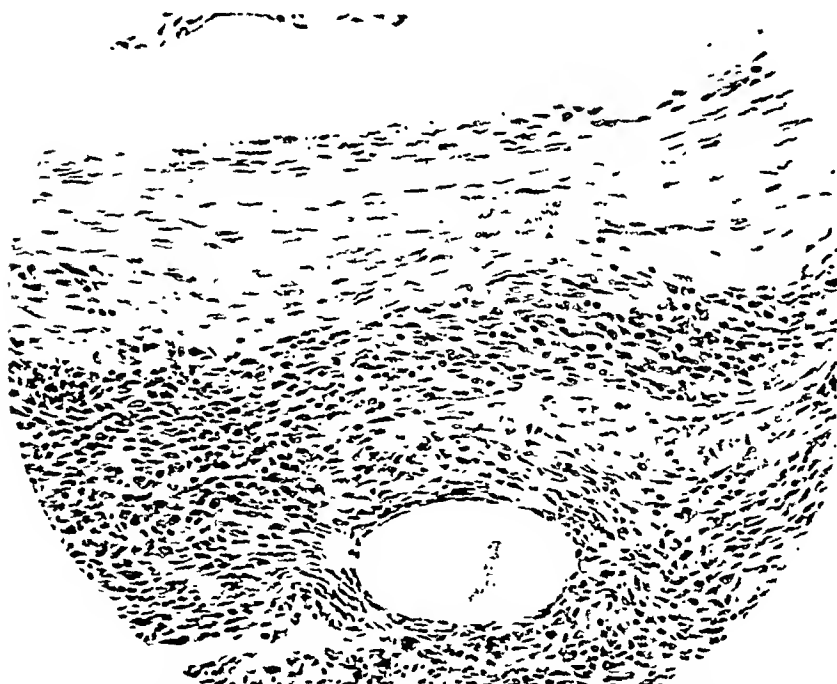


Fig. 2.—Higher magnification of the tumor. The oval space, lined with endothelium, suggests possibly an attempt to form a synovial cavity.

The right inguinal lymph nodes had become slightly enlarged following the biopsy and had been excised on November 17. They were free of tumor. Also, 900 r (3 exposures, 140,000 volt, 50 cm. distance, A. L. filter) had been given between November 15 and November 22, with the vague idea of doing something possibly useful until a final decision had been made.

Finally, amputation at mid-thigh level was performed on December 4. Operation and postoperative course were uneventful. The infant has been seen at regular intervals, the last time on Dec. 21, 1948. He has developed normally and is in good health.

The skin over the tumor area in the operative specimen was slightly pigmented and scaling. The tendons were surrounded by light brown and pinkish mottled glistening tissue. The periosteum and bone were not involved. Microscopically, the tendons were surrounded by sheathlike masses of tumor cells as described which seemed intimately connected with the tendon sheaths. Hemosiderin was present in moderate amounts. The connective tissue was somewhat edematous. No cellular changes attributable to radiation as applied were noted. The diagnosis was congenital spindle-cell sarcoma of foot, arising probably from tendon sheath.

#### DISCUSSION

Little need be said about the histologic aspects of this case. Slides were submitted to several prominent pathologists who all concurred on the diagnosis of sarcoma. The arrangement of the tumor cells around the tendons and their continuity with the tendon sheath suggests that the tumor developed from these structures. The hemosiderin and inflammatory reaction are attributed to the trauma produced by the attempt to crush the mass. No histologic evidence of response to roentgen rays was seen but the amount applied was too small to allow drawing any deductions regarding its effectiveness. However, all consultants agree that a tumor of this type is radio-resistant.

In order to evaluate more intelligently the selection of treatment in congenital sarcoma and the prognosis attached to it, Table VII of Wells' paper was rearranged and the case reported by Paek and Anglem and the present case were added. The untreated and treated cases were separated and grouped according to the location of the tumor in the extremities or elsewhere. The treated cases were also arranged according to the type of therapy. (See Table I.)

The following conclusions can be drawn:

A. All untreated cases of congenital sarcoma die, irrespective of location and histologic type.

B. Treatment and results obtained differ sharply between congenital sarcoma located in the extremities and that located elsewhere in the body.

1. With proper treatment, the prognosis for congenital sarcoma of the extremities is excellent. Ten patients out of twelve are reported well for periods up to ten years. With the outcome unknown in one instance, there remains only one case with fatal outcome (No. 21). This patient died immediately following amputation which had been delayed until he was 16 months old. Previous prolonged roentgen therapy had proved ineffective.

TABLE I\*

NO	LOCATION	HISTOLOGIC TYPE	THERAPY	OUTCOME	REMARKS
UNTREATED CASES					
1	Thigh	Fibrosarcoma	None	Unknown	Size of infant's head at birth
2	Thigh	Periosteal	None	Died	
3	Orbit	Round cell	None	Died	
4	Orbit	Round cell	None	Died	
5	Brain	Angiosarcoma	None	Died	
6	Neck	Angiofibrosarcoma	None	Died	
7	Skin	Round cell angiosarcoma	None	Died	
8	Pancreas	Lymphosarcoma	None	Died	
9	Small bowel	Round cell or angiosarcoma	None	Died	
10	Prostate	Rhabdomyosarcoma	None	Died	
TREATED CASES					
<i>Tumor Located in Extremity</i>					
11	Upper arm	Oat cell	Excision	Recovered	Follow up 2 years
12	Calf	Spindle cell	Excision	Unknown	
13	Humerus	Spindle cell	Amputation	Recovered	Follow up 10 years
14	Fibula	Spindle cell	Amputation	Recovered	Follow up 4 years
15	Tibia	Fibrosarcoma	Amputation	Recovered	Follow up 8 years
16	Foot	Fibrosarcoma	Amputation	Recovered	Follow up 8 months
17	Foot	Spindle cell	Amputation	Recovered	Follow up 1 year
18	Foot	Sarcoma	Amputation	Recovered	Not stated
19	Humerus	Periosteal	Excision and radiation	Recovered	31 months
20	Femur	Spindle cell	Radiation plus amputation	Died	Not stated
21	Forearm	Spindle cell	Radiation	Recovered	Died postoperative after unsuccessful radiotherapy
22	Leg	Liposarcoma	Radiation	Recovered	Follow up 4 years
<i>Tumor Located in Places Other Than the Extremities</i>					
23	Tongue	Spindle cell	Excision	Unknown	
24	Tongue	Spindle cell	Excision	Died	
25	Tongue	Round and spindle cell	Excision	Died	
26	Axilla	Fibrosarcoma	Excision	Unknown	Metastases present
27	Subcutis	Round cell	Excision	Died	Metastases present
28	Shoulder	Fibrosarcoma	Excision	Died	
29	Vulva	Myosarcoma	Excision	Died	Aged 4 months from congenital heart disease Metastases present
30	Parotid	Angiosarcoma	Excision	Recovered	Only short follow up
31	Upper lip	Spindle cell	Excision plus radiation	Recovered	Follow up 8 months

\*Rearranged from Wells' publication to which the reader is referred for details

All six patients upon whom amputations were performed recovered

Excision was apparently sufficient for two patients, one of whom also received postoperative radiation

One patient with liposarcoma of the leg was treated by radiation alone and was well after four years

With exception of this last case, the congenital sarcomas of the extremities form a quite homogenous histologic group of a type that is generally con-

sidered radioresistant. However, there are not sufficient recent data available to determine definitely the role of radiotherapy in these lesions. Surgical treatment, on the other hand, has given uniformly good results and must be considered the treatment of choice, at least for the time being. Conceivably this attitude will require revision once results comparable to those obtained by surgery can be demonstrated by radiotherapists. Preoperative and post-operative radiation does not seem to add anything and, therefore, is not indicated.

It is difficult to select a standard operative procedure in these cases. None of the congenital sarcomas of the extremities has been found to spread to the lymph nodes. None has recurred locally; none has metastasized. The size and location of the tumor and the small terrain available in a newborn infant will make complete excision probably impractical in the majority of instances. Amputation on the other side has given uniformly good results. It should be done at the lowest possible level. In this way, one could justly hope for a permanent cure and at the same time the loss of limb kept at a minimum. In retrospect, the amputation as carried out in the present case, must be considered needlessly high.

Exarticulation would appear required only if amputation between tumor and joint is technically impossible.

2. Congenital sarcoma in locations other than the extremities has a much graver outlook. Only two out of nine patients are reported as cured. A third patient died when four months old from congenital heart disease at which time the tumor of the vulva had not recurred, but metastases were present. Histologically, these tumors are of greater variety. Local recurrences and metastases are more frequent. Complete surgical removal is impossible in many instances for technical reasons and incomplete removal has given poor results. It is possibly in this group that modern methods of radiation can be expected to improve the up-to-now disappointing picture.

#### SUMMARY

Congenital sarcoma is a rare lesion. A case of congenital sarcoma of the foot is reported. Analysis of all reported cases shows that congenital sarcoma of the extremities has a surprisingly good prognosis. Treatment is surgical. Amputation at the lowest possible level appears to be the most sensible approach. Radiation is no substitute for surgery but its possibilities cannot be fairly judged at this time. Congenital sarcoma in locations other than the extremities has a much graver prognosis. Surgical treatment is usually impractical or ineffective. Radiotherapy is considered preferable in this group whenever complete removal is impossible.

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# CIRRHOSIS OF THE LIVER IN CHILDREN

## A CLINICAL AND PATHOLOGIC STUDY OF FORTY CASES

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### INTRODUCTION

MANY papers have appeared during the past thirty years discussing the several types and characteristics of cirrhosis of the liver. However, there is only scattered information pertaining to such pathologic conditions in children. The available reports stress that the disease is uncommon in children. Most reports deal with a particular type or phase of cirrhosis and include only a few isolated, often unclassified, cases. No comprehensive report on the subject of juvenile cirrhosis is available. Nevertheless, as more data accumulate it appears that cirrhosis in children is not uncommon. Clinicians should be alert to recognize it and to understand its relationship to the various syndromes in which it may appear. Although juvenile cirrhosis morphologically does not often differ significantly from the disease in adults, there are certain features in regard to etiology, incidence, and pathogenesis that are more or less peculiar to children. For a discussion of hepatic cirrhosis in adults the reader is referred to the recent paper by Karsner.<sup>1</sup> The purpose of the present paper is to classify and correlate available data on the subject of juvenile cirrhosis and to report the cases studied at the St. Louis Children's Hospital. The peculiarities and problems which characterize the disease in children will be stressed.

*Definition.*—Cirrhosis is a term which should be applied only to the liver. In this paper cirrhosis applies to all sclerotic conditions of the liver in which there is destruction of the liver parenchyma with fibrous connective tissue replacement. The majority of patients whose cases are herein presented have had cirrhosis to the extent that the scarring could be recognized by gross examination. Any case in which fibrosis was questionable on examination of microscopic sections is excluded.

It is considered that when cirrhosis afflicts an individual under the age of 15 years, it can be considered juvenile cirrhosis. The upper limit in age for admission to The St. Louis Children's Hospital is 15 years, so this age limit was arbitrarily selected. The age of the oldest patient studied was 14 years.

*Incidence.*—Cirrhosis in children, especially the "biliary type" is a fairly common disease in India according to the reports of Ghose,<sup>2</sup> Radhakrishna Rao,<sup>3</sup> Prabhu,<sup>4</sup> and Chandhuri.<sup>5</sup> In contrast, reported cases of juvenile cirrhosis in Europe and America are uncommon. The reason for this difference is not clear. Both a family tendency and multiple dietary deficiencies seem

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to be more consistently present in India than in temperate climates. Karsner<sup>1</sup> quotes De Josselin de Jong<sup>6</sup> as placing the incidence in children between 0.5 and 4.4 per cent of all cases of cirrhosis reported at the first conference of the International Society for Geographic Pathology in 1931. Passini<sup>7</sup> cited six cases of cirrhosis among 160,000 children, but the autopsy rate is not specified. The combined figures of Menne and Johnston<sup>8</sup> and of Karsner<sup>1</sup> show an incidence of five cases of juvenile cirrhosis in 211 autopsied cases of cirrhosis of all ages. Nodular cirrhosis in children is especially rare. Further comments on its incidence will be made under a separate heading.

In the twenty-six years preceding 1947 there was a total of 82,866 admissions to the St. Louis Children's Hospital with 4,669 deaths and 2,441 autopsies. Among these there was a total of forty cases of cirrhosis, thirty-one confirmed by autopsy and nine proved by laparotomy with biopsy of the liver. There have been several additional cases diagnosed clinically as cirrhosis but without microscopic confirmation. They are not included in this report.

*Familial Tendency.*—The reports of Ghose,<sup>2</sup> Mackenzie,<sup>9</sup> and Jollye<sup>10</sup> indicate that a prominent familial tendency exists in those cases occurring in India and Mexico. Such a trait is also reported in America and in Britain by Ely,<sup>11</sup> Gunn,<sup>12</sup> Bridgeman and Robertson,<sup>13</sup> Yater and Saccardi,<sup>14</sup> and by Jameson and Savarese.<sup>15</sup> It is felt that some examples of cirrhosis may represent instances of incompatibility of blood group between mother and fetus (erythroblastosis fetalis) in which the family nature is well established and understood. Congenital biliary atresia, like other anomalies of development, shows a tendency to be familial. This is reported to be true of nodular cirrhosis also.

In the forty children herein reported all have come from separate families but a few of the histories suggest that more than one member of a family have been afflicted with the same disease. This is true especially in some of them classed under the heading of erythroblastosis fetalis.

*Classification.*—It is desirable in juvenile cirrhosis, as in all diseases, to make an etiological classification. Unfortunately this is not possible because of insufficient knowledge. In previous reports all cirrhosis in children is placed under a single classification of "juvenile cirrhosis" except for the few instances where a "biliary" or "nodular" type is distinguished. The following classification will be followed in the presentation of this series. It is a combination of the ones used by Moore,<sup>16</sup> and by Karsner<sup>1</sup> for adults, with the addition of erythroblastosis. It is adaptable to juvenile cases and includes most of the following types described in adults:

- Obstructive biliary cirrhosis
- Nodular (Laennec's, portal, atrophic, etc.) cirrhosis
- Postnecrotic cirrhosis
- Congestive ("cardiac") cirrhosis
- Erythroblastosis fetalis
- Hepatolenticular degeneration
- Unclassified cirrhosis

The existence of other types of cirrhosis, e.g., syphilitic, pigmentary, lipid, and zooparasitic is recognized, but these are not represented in our series.

#### OBSTRUCTIVE BILIARY CIRRHOSIS

Obstruction to the flow of bile from the hepatic cells into the duodenum may result from a variety of causes. The common cause in children is congenital atresia of the bile passages. Rare causes include stones in the common duct, enlarged lymph nodes about the major bile passages, inspissated viscid bile in the bile passages, and occlusion of the extrahepatic duct lumina by pressure or infiltration of tumor tissue. The site of the atresia is usually in the extrahepatic bile passages according to Stolkind,<sup>17</sup> Holmes,<sup>18</sup> and Ladd.<sup>19</sup> Authentic examples where the obstruction is located in the intrahepatic portions of the ducts are recorded by McClendon and Graham,<sup>20</sup> and by Parsons and Hickmaus.<sup>21</sup>

The best explanation for congenital anomalies of the bile ducts is that which attributes them to incomplete or improper embryonic development. The factors that influence or control embryonic development are not understood. It is noteworthy that anomalies of the bile passages are sometimes associated with other anomalies, especially of the heart.<sup>22</sup> A familial tendency is sometimes shown.<sup>23, 24</sup> The reported incidence of congenital atresia of the biliary system is not large. Motsay and May<sup>25</sup> state that up to 1945 only about 200 cases were described in the American literature. Donovan<sup>26</sup> reported an incidence of sixteen cases in 21,000 admissions at the New York Babies' Hospital over a ten-year period. In 2,441 autopsies at the St. Louis Children's Hospital in the last twenty-six years only five patients with demonstrable atresia of the bile passages other than the gall bladder or cystic duct are recorded. In one (Case 7, Table I) the obstruction was due to fibrosis of aberrant pancreatic tissue in the duodenal wall. Two additional children had laparotomies with liver biopsy during the same period. These eight cases are included in this report. Other instances diagnosed clinically and still others where laparotomy was performed but without liver biopsy are not included in this study.

It is important to remember that all patients with congenital anomalies of the bile ducts that obstruct the flow of bile from the liver develop cirrhosis if they live any appreciable length of time. Chesterman<sup>27</sup> in his article on congenital bile duct atresia states, "The liver is invariably involved with chronic obstructive cirrhosis unless the cystic duct or the gallbladder only are atretic." It is also important to stress that the ultimate termination of all unoperated patients with complete obstruction of the ducts is death early in life. Most patients die before eight months of age although the one reported by Finlayson<sup>28</sup> lived three years and three months. This seems to be a record. Our patient that lived longest with complete obstruction of the major bile ducts died at the age of 30 months. One in this series had complete obstruction of the common duct but an anomalous accessory duct directly from the liver to the ampulla of the gall bladder. The lumen of this accessory duct was much

TABLE I. SUMMARY OF FINDINGS IN OBSTRUCTIVE BILIARY CIRRHOSIS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8
Age at onset of jaundice	10 days	1 day	9 days	11 mo.	3½ mo.	2 to 3 week	5 years	7 days
Age when first seen	5 mo.	8½ mo.	7 mo.	2½ yr.	3½ mo.	6 week	5½ yr.	1 mo.
Age at death or biopsy	5 mo.	9 mo.	7 mo. 1	2½ yr. 2	1½ yr. 3	2 mo.	5½ yr.	5 mo.
Hepatomegaly	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Splenomegaly	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Ascites, in cubic centimeters, if known	200	100	No	1,600	1,600	No	Slight	200
Prominent abdominal veins	Yes	Yes	Yes	No	Yes	No	Yes	No
Purpura tendency	Yes	No	No	No	No	Yes	Yes	Yes
Hemorrhage in gastrointestinal tracts	No	Yes	No	No	No	No	No	No
Malnutrition	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Respiratory infections	Yes	Yes	Yes	No	Yes	No	No	Yes
Hernia	Umbilical	No	No	Umbilical	No	No	No	No
Hemoglobin in grams per 100 c.c.	8.0	7.6	10.0	7.47	5.87	12,700	5.87	7.86, 7
Leucocyte count	16,500	25,000	11,500	11,350	25,000	More than 307	71,000	28,350
Clotting time in minutes	-	-	3½	5	-	307	1½	2
Bleeding time in minutes	-	-	3	2	3	Prolonged	2½	1½
Prothrombin time	-	Prolonged	-	Prolonged	Normal	-	-	Normal
Serum albumin in grams per 100 c.c.	-	4.6	-	3.0	2.50	-	3.09	3.16
Serum globulin in grams per 100 c.c.	-	2.85	-	3.6	4.20	-	4.57	2.34
Serum total protein	-	7.45	6.05	6.67	6.70	-	7.03	5.50
Icterus index	118	1.507	92	110	120	-	35	160
Van den Bergh	Direct	-	-	Direct	Direct	Direct	Direct and indirect	-
Urine bilirubin	Present	Present	-	Present	Present	Present	Present	Present
Urine urobilinogen	-	Absent	-	-	Absent	Absent	-	-
Clay colored stools	Present	Present	Present	Present	Intermittent	Present	Present	Present

1Date and circumstances of death not known.

2Died at 3 years, 10 months, at home.

3Died at 1 year 8, 8 months, at Homer G. Phillips Hospital.

4At autopsy.

5At laparotomy.

6Nucleated red blood cells found in peripheral blood.

7Where more than one determination is reported, the most extreme value is given.

8Serologic test for syphilis was negative in all cases.



smaller than the usual common duct. This patient lived with partial obstruction to be 4 years, 9 months old.

In obstructive biliary cirrhosis the etiology and the pathogenesis are well understood. The morphologic findings are quite uniform. This form of cirrhosis has been studied and reproduced experimentally. For the surgical aspects of this disease and the pathology other than the cirrhosis the reader is referred to the articles by Ladd,<sup>19</sup> Amberg,<sup>22</sup> Behrend,<sup>20</sup> and to Ladd and Gross.<sup>30</sup>

The clinical findings in obstructive biliary cirrhosis include a progressive jaundice that begins in the congenital cases a few days after birth. There are clay-colored stools, dark urine, an enlarged and palpable liver, and a moderate splenomegaly. Ascites of significant degree is not uncommon, and the superficial abdominal veins frequently are prominent. Nutrition usually is good. There is an abnormal susceptibility to respiratory infections. The laboratory findings are those of complete obstructive jaundice, viz.; a high ieterus index, excessive bile in the urine, a direct Van den Bergh reaction, decreased liver function late in the disease as indicated by special tests, and, most important, the presence in the urine of no more than traces of urobilinogen, or none at all.

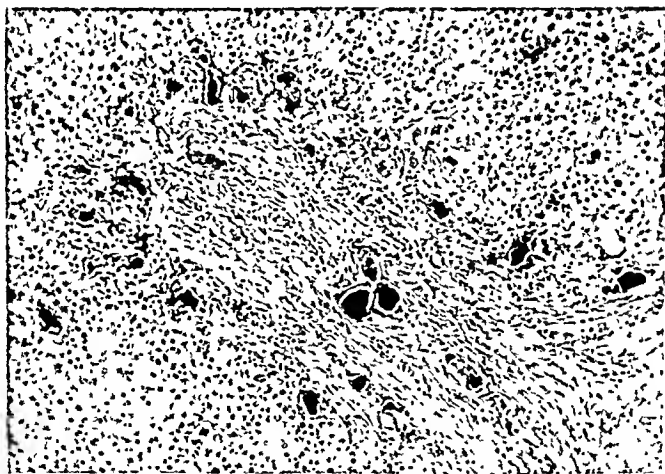


Fig. 1.—R. W. Obstructive cirrhosis, showing great increase in periportal connective tissue with inflammatory infiltration; bile pigment chokes the ducts and is taken up by Kupffer cells. (Case 9, Table I.) (×100.)

The differential diagnosis includes ieterus neonatorum, erythroblastosis fetalis, jaundice due to sepsis and to congenital syphilis. Except for ieterus neonatorum the jaundice of these conditions may be the complete obstructive type for a transient period.

The gross pathologic findings, in addition to the assorted malformations of the bile ducts, include a generalized ieterus of the tissues and a large nodular liver with variable amounts of scarring. The microscopie picture is that

of an interlobular fibrosis, bile stasis, and, to a limited degree, the presence of lymphocytes and monocytes. The architecture of the liver may be somewhat more distorted in children than in obstructive cirrhosis in adults. Table I shows the clinical and laboratory data on eight cases of obstructive biliary cirrhosis. A characteristic section showing the usual microscopic features is shown in Fig. 1.

#### DIFFUSE NODULAR CIRRHOSIS

Diffuse nodular cirrhosis, also known as Laennec's, portal, atrophic and alcoholic cirrhosis, and hobnail liver, is a classification based purely on morphologic findings. This is not ideal. Improvement awaits a better knowledge of its etiology and pathogenesis. The pathologic anatomy does not differ in children from adults. Presumably the same etiologic factors (alcohol, dietary deficiency, infection, hepatotoxic agents, etc.) hypothesized as playing a role in the production of nodular cirrhosis in adults, may be the factors responsible for the production of juvenile nodular cirrhosis. Alcohol must be a less common casual agent.<sup>31</sup> Several writers<sup>12, 13, 15, 31, 32</sup> state that there is a tendency for the disease to occur in families. None of the cases herein presented show such a trait. The incidence of the disease in children is less than in adults. Bridgeman and Robertson<sup>13</sup> in 1932 reported the fourteenth American case of nonalcoholic nodular cirrhosis. To our knowledge none have been reported since. There are also about fifteen cases reported of alcoholic nodular cirrhosis. In the past twenty-six years there have been eleven cases at the St. Louis Children's Hospital which by biopsy or at autopsy have presented the characteristic tawny, firm, grossly nodular liver, splenomegaly, and portal varices. The microscopic findings are those of an extensive perilobular fibrosis, focal regeneration of parenchymal cells, and chronic inflammatory cell infiltration of the scar tissue. The history in some cases suggests possible casual agents. They may be only coincidental, however, and unrelated to the fibrosis of the liver. Selected case reports are presented below, the numbers corresponding to those in Table II.

CASE 1.—C. B., aged 9, a white boy, entered the hospital on June 13, 1923, having been well until the appearance of anorexia and progressive weight loss eight months before. The abdomen had gradually enlarged.

The family and past histories were unrevealing save that at the age of 4 years the child had been very ill for a month with "trench fever." The father had died from the same disease.

At the time of admission the child was extremely emaciated with a huge, protruding abdomen that was covered with dilated superficial veins. There was evidence of ascites. After paracentesis the spleen was found to be greatly enlarged. The liver also was enlarged, hard, and nodular. Hemorrhoids were prominent. These findings confirmed by an exploratory laparotomy, together with gross glycosuria and hyperglycemia, led to the diagnosis of diabetes mellitus and cirrhosis of the liver. A section of the liver is shown in Fig. 2.

CASE 3.—W. H., a Negro boy aged 9 years, was the only child of healthy parents. The mother's second pregnancy resulted in a miscarriage at two

TABLE II. SUMMARY OF FINDINGS IN NODULAR CIRRHOSIS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9	CASE 10	CASE 11
Age at onset of symptoms	8 yr.†	17 mo.†	8½ yr.	5 yr.	9 yr.	8 yr.	13 yr.†	3½ yr.	Infancy?†		
Age when first seen	9 yr.	17 mo.	9 yr.†	5½ yr.	9½ yr.	8 yr.	13 yr.	7 yr.	6½ yr.	11 yr.	3 mo.†
Age at death* or biopsy†	9 yr.*	9 yr.*	9 yr.†	6½ yr.†	9½ yr.*	8 yr.*	13 yr.*	8 yr.†	6½ yr.†	14½ yr.*	4 mo.*
Hepatomegaly	Present‡	Present	Present	Present‡	Present	Present	Present	Present	Present	Absent	Present
Splenomegaly	Present	Present	Present	Present‡	Present	Present	Present	Present	Present	Absent	Absent
Ascites, in cubic centimeters, if known‡	5,000‡	600‡	70	700‡	400‡	2,000‡	None	None	None	None	300‡
Jaundice	Absent	Absent	Present	Present	Present	Present	Present	Present	Absent	Present	Absent
Hemorrhage in gastrointestinal tract‡	Present	Present	Present	Present	Present	Present	Present	Absent	Absent	Present	Absent
Hemorrhagic tendency elsewhere	Absent	Present	Present	Present	Present	Present	Present	Absent	Absent	Present	Absent
Prominent abdominal veins	Present	Absent	Present	Absent	Absent	Present	Present	Absent	Absent	Present	Absent
Malnutrition	Present	Present	Absent	Absent	Absent	Present	Questionable	Absent	Present	Absent	Absent
Anorexia	Absent	Present	Absent	Absent	Present	Present	Absent	Absent	Present	Absent	Absent
Respiratory infections	Yes	Present	Absent	Absent	Present	Present	Present	Absent	Present	Absent	Present
Drowsiness	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Absent	Present
Hemoglobin in gram per 100 c.c.	-	-	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Leucocytes‡	9,200	14,100	20,000	29,600	5,700	14,400	7.9	10.5	9.0	8.0	- <sup>13</sup>
Clotting time in minutes	-	-	-	20:12	8	13	3:100	1:300	14,100	3,000	34,500
Bleeding time in minutes	-	-	-	9:12	5:50"	6	25:100	42:700	-	3½	-
Prothrombin time	-	-	-	-	5:50"	6	2	12:12	-	6½	-
Serum albumin in gram per 100 c.c.	-	-	-	-	Prolonged	Prolonged	4	4	11	Normal	-
Serum globulin in gram per 100 c.c.	-	-	-	-	1.92	5.20	-	-	-	3.4	-
Serum total protein	-	-	-	-	6.79	1.95	-	-	-	3.8	-
Fetus index	-	-	-	9.90	8.71	7.16	-	-	-	7.2	-
Van den Bergh	-	-	270:12	75:12	78	240:12	15:12	3	-	25:12	4:30
Urine bilirubin	-	-	Immediate direct, indirect	-	Immediate direct	-	-	Negative	-	Immediate direct	-
Urine urobilinogen	-	-	Present	Present	Present	Present	-	-	-	Slight	-
Clay-colored stools	-	-	Present	-	Present	Present	-	-	-	-	-
Clinical diagnosis made or suggested	Absent	Absent	Present‡	Absent	Present‡	Present‡	Absent	Absent	Absent	Present	Absent
	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No

Had had three previous admissions for hemorrhaphy, pneumonia, and tuberculosis, but no evidence of cirrhosis was then reported.

†Died at age 22 with advanced cirrhosis.

‡Living and well when first seen in 1910, aged 9 years.

§Liver regressed in size subsequently.

¶When regressed in size subsequently.

\*\*Maximum value given.

††At laparotomy.

†At autopsy.

‡Some, but

††Where several values are reported, the most abnormal is given.

‡Stool contained bile at times.

††At death.

†††At biopsy.

tendency rather than ruptured varices.

†††Where several values are reported, the most abnormal is given.

‡Stool contained bile at times.

††At death.

†††At biopsy.



Fig. 2.—C. B. Nodular cirrhosis, showing increase in periportal connective tissue, round cell infiltration, dilatation of the sinusoids, and sharp demarcation of the lobules. (X100.)

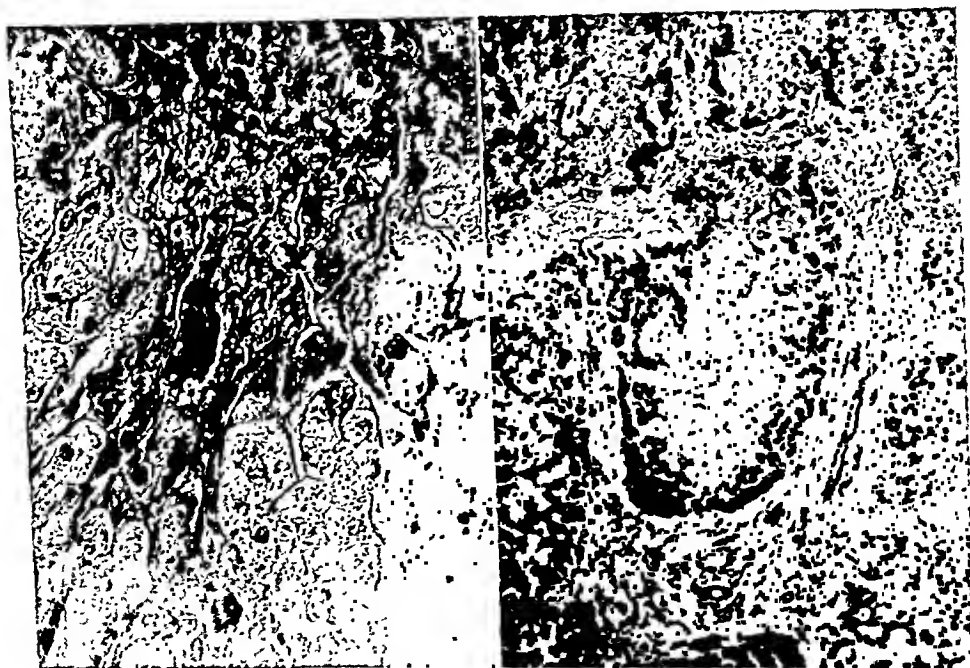


Fig. 3.

Fig. 4.

Fig. 3.—W. H. Biopsy sixteen months before death, showing periportal blood extravasation and the swollen, coarsely granular cytoplasm of the parenchymal cells. No evidence of cirrhosis. (Mallory stain, X100.)

Fig. 4.—W. H. Autopsy showing islands of liver cells surrounded by interlacing strands and large areas of fibrosis with great distortion of architecture. The fibrous tissue is relatively cellular and shows round cell infiltration. Sinusoids are dilated and there is cloudy swelling of liver cells but no frank necrosis. (See Fig. 3, sixteen months earlier.) (X100.)

months. The family history otherwise is unrevealing. He was first admitted in 1927 for bilateral hernioplasties. Pneumonia from which he recovered complicated the postoperative course. He again had pneumonia in 1930 and in 1931. Soon after, a diagnosis of pulmonary tuberculosis was made. After treatment for two and one-half years in a sanatorium he was discharged as having an arrested case of tuberculosis. Liver disease up until this time was not diagnosed. In 1934, at the age of 9 years, he was readmitted to Children's Hospital. Several months after discharge from the sanatorium he had developed gradually a progressive jaundice. A week before admission he had become listless, sluggish, and his legs ached. The day before admission he experienced visual disturbances, nausea and vomiting, and headache. His stools were flecked with blood.

The patient was fairly well nourished, markedly jaundiced, and had a mild rhinopharyngitis with a low-grade fever. His liver was palpable but not considered enlarged. The spleen was very large. Hematologic findings were within normal limits save for leucocytosis. His tuberculin reaction was 4 plus, and serology was negative.

Laparotomy revealed a spleen twice the normal size and a grossly smooth but firm liver. A biopsy of the liver was taken (see Fig. 3).

Sixteen months later he was readmitted. Jaundice had persisted, visual disturbances which had cleared returned, and he developed a marked tremor of the hands. On several occasions he had nosebleed. Mental confusion was marked. Physical examination revealed a large, hard liver and a prominent splenomegaly. Ascites was present. Anemia was marked. Laparotomy revealed a nodular cirrhotic liver and a huge spleen. The contemplated splenectomy was abandoned because of uncontrollable hemorrhage. The patient died a few hours later.

Autopsy disclosed an advanced nodular cirrhosis of a 1,100 gram liver. The spleen weighed 700 grams. Sections of the spleen showed prominent sickling of the red blood cells. For the microscopic appearance of the liver see Fig. 4.

CASE 4.—S. S., a girl, aged 5, was admitted to the hospital with a diagnosis of scarlet fever and a past history of repeated epistaxes. An incidental finding was that of a marked splenomegaly. The day after discharge she had another severe nosebleed and was readmitted for a day.

Nine months later she was again readmitted. Her complaints were anorexia of one year's duration, repeated epistaxes, and epigastric pain with vomiting. Epistaxes had been frequent for a month. There was generalized lymphadenopathy, persistent low-grade fever, and mild icterus. The liver was not felt. The spleen extended only 3 fingerbreadths below the costal margin. The patient was discharged unimproved after two weeks. She did poorly from that time on; she was hospitalized on two other occasions; death resulted from pneumonococcus pneumonia in December, 1939. On the final admission she had clinical ascites confirmed by autopsy. Her liver, which was of average size, was nodular and grossly cirrhotic. Autopsy section (Fig. 6) of the liver showed marked advancement of the cirrhotic process previously seen in the biopsy section in Fig. 5.

*Discussion.*—The etiology of the cirrhosis in these cases of nodular cirrhosis is still obscure. It is true that several of the patients had acute infectious disease (trench fever, pneumonia, tuberculosis, influenza, etc.) prior to the onset of clinical liver disease. Whether these infections were specific or

remote causes of liver damage is problematical. The likelihood that they were merely coincidental is great. In several cases dietary deficiency may have been a factor. Case 2 is known to have had rickets years before the clinical signs of cirrhosis appeared. The evidence that a deficient diet played a role is not at all convincing. The relationship of tuberculosis and diabetes mellitus to cirrhosis where both diseases existed is probably only coincidental. Case 2 also had congenital heart disease but only terminally was there any evidence of cardiac decompensation, so it is believed the extensive cirrhosis seen at autopsy was not the result of chronic passive congestion. No statement relative to alcohol ingestion by these children is included in the histories. The possibility of erythroblastosis fetalis being the initial underlying cause of

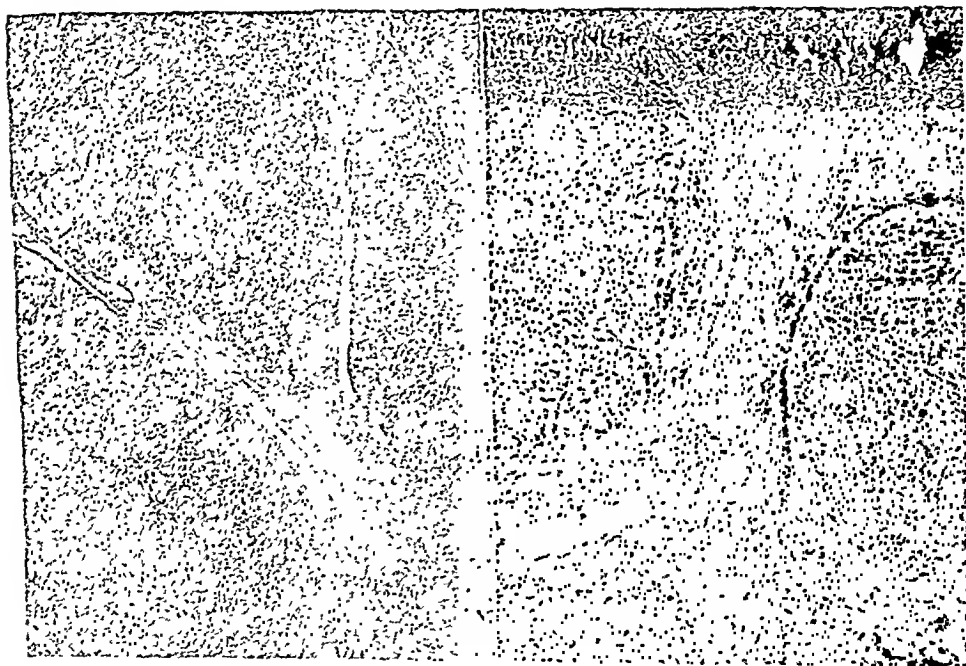


Fig. 5.

Fig. 6.

Fig. 5.—S. S. Biopsy, nodular cirrhosis, showing diffuse portal scarring with moderate lymphocytic infiltration. ( $\times 60$ .)

Fig. 6.—S. S. Autopsy, showing great increase in fibrosis by comparison with Fig. 5 nine and one-half months earlier. Hepatic cells embedded in the connective tissue are rare, but there are many bile ducts and small collections of leucocytes. (Masson stain,  $\times 60$ .)

the disease in some of these patients cannot be ignored. Three patients have family histories of miscarriages. There are no available Rh studies to confirm a suspicion of Rh incompatibility in any of the eleven cases. It is worth noting that sickle cell anemia and cirrhosis are sometimes associated. Such was the case in one of these eleven patients. The mechanism of liver damage might be similar to that postulated for erythroblastosis fetalis. The surgery could occur during a sickle cell crisis.

Most of these patients presented the clinical picture that was once called "Banti's disease." Some of the less advanced cases, however, did not have anemia and leucopenia. Ascites was present in seven patients. Jaundice was absent in three cases, including one of the most severe. The very large spleen found in all but one was in most instances the result of portal hypertension which results from obstruction of the portal blood flow through the cirrhotic liver. The details of this mechanism are explained by Moore.<sup>16</sup> Case 2 is known to have had a large spleen seven years before she developed further clinical evidence of cirrhosis. Case 8 had bleeding tendencies and a splenomegaly three years before becoming ill. It seems unlikely that cirrhosis per se so early in the disease caused hypertension and splenomegaly.

It seems logical to conclude from this study as well as from the findings of other authors that nodular cirrhosis may be an advanced stage of some process that was precipitated by various etiologic agents. If more were known of the pathogenesis these patients might belong under the classification of erythroblastosis fetalis or postnecrotic cirrhosis.

*Diagnosis.*—A history of gradual, usually painless swelling or enlargement of the abdomen, often associated with swelling of the lower extremities, is the most common subjective symptom. There is often a long story of anorexia, weakness, and gradual weight loss. Attacks of jaundice in the past or beginning with the onset of the present illness are quite common. Vague abdominal pain, discomfort, and distress may be present in these patients. Both drowsiness and irritability frequently are mentioned. A history of bleeding from the nose, esophageal varices, or hemorrhoids is consistent enough to be helpful.

All of these patients save one had a splenomegaly. All but one had a palpable hard liver. Ascites is a common finding and often is associated with dependent edema. Prominent superficial veins occur but the so-called venous spiders have not been a finding of any frequency in these or other reported cases in children. Poor nutrition and susceptibility to infections are consistent findings. The age of onset in our group has varied from less than one year to 13 years.

In those children where the liver damage is extensive enough, liver function tests will show evidence of decreased liver function. Low total proteins with increase in the globulin fraction and decrease in albumin is a common finding where there is ascites or dependent edema.

X-ray studies may be utilized to demonstrate esophageal varices and an enlarged spleen also may be shown.

Biopsy of the liver is the only method whereby an accurate diagnosis can be made. It should be resorted to unless there are strong contraindications. Laparotomy is the ideal method of securing a liver specimen. It is safe, an adequate specimen can be obtained, and the liver can be inspected grossly. However, Hoffbauer, Evans, and Watson<sup>23</sup> strongly recommend needle biopsy. They feel it is indicated if liver function tests prove equivocal and laparotomy seems inadvisable.

## ERYTHROBLASTOSIS FETALIS

Several authors have reported examples of juvenile cirrhosis in which there was a history of severe neonatal jaundice.<sup>34-38</sup> Many of them may well have been the one clinical form of erythroblastosis known as icterus gravis. Hawksley and Lightwood,<sup>39</sup> in 1934, suggested and gave evidence that some cases of juvenile cirrhosis are associated with erythroblastosis. Poynton and Wyllie<sup>10</sup> point out that in those infants with icterus gravis who do not die in the first few days after birth, the microscopic post-mortem details are strongly suggestive of early biliary cirrhosis. Braid and Ebbs,<sup>41</sup> in 1927, and Webster,<sup>42</sup> in 1938, reported instances of cirrhosis in children that followed neonatal icterus gravis. Henderson<sup>43</sup> has recently reported four stillborn infants who, in addition to having the findings of erythroblastosis, also had marked hepatic cirrhosis. The incidence of erythroblastosis is estimated to be one per 200 births in American infants. The incidence of cirrhosis following erythroblastosis must be rare, as only a very few cases are reported in the literature.

From our studies we have arrived at the conclusion that many cases of juvenile cirrhosis in early adulthood may be a part of or the end result of fetal erythroblastosis. Recent knowledge about Rh factors and anti-Rh agglutinins in the blood<sup>44-46</sup> makes it possible to diagnose the less typical forms of the disease (forms without anemia, without erythroblastosis, with complete obstructive jaundice, and with only mild abortive manifestations). The pathogenesis of erythroblastosis as given by Davidsohn<sup>46a</sup> postulates that extramedullary hematopoiesis and anoxemia result in liver damage. In examining the slides on our cases we have been impressed with the fact that the distribution of the fibrosis is very similar to that of the extramedullary hemopoietic centers and that fibrosis about the existing centers, when present, is very noticeable.

TABLE III. SUMMARY OF FINDINGS IN ERYTHROBLASTOSIS FETALIS

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
Familial incidence	Absent	Present	?	Absent	Absent
Life span	2 mo.	2 days	1 day	9 weeks	10 weeks
Age at onset of jaundice	3 days	1 day	?	1 mo.	1 day
Purpuric tendency	Present	Present	Present	?	Absent
Hepatomegaly	Present	Present	Present	Present	Present
Splenomegaly	Present	Present	Present	Present	Present
Edema	Absent	Slight	?	Absent	Absent
Hemoglobin in gram per 100 c.c.	9.0	11.3	17.8	9.5	15.6
Leucocytes	52,000	64,400	49,600	17,800	94,200*
Leucemoid blood picture	Present	Present	Present	Absent	Present
Nucleated R.B.C. in circulation, per 100 W.B.C.	27	4	10	Present	5
Icterus index	115	150	-	65	-
Blood Kline	Negative	Negative	Negative	Negative	Negative
Mother Rh-negative, father and child positive	Yes	Yes	Not known	Not known	Not
Extramedullary hemato-poiesis	Present	Present	Present	Present	Absent
Biliary stasis	Present	Present	Present	Present	Present
Hemosiderosis	Present	Present	Present	Absent	Present
Cirrhosis	Marked	Slight	Slight	Marked	Moderate

\*This patient had bilateral otitis media, diarrhea, and a subcutaneous abscess.  
†Rh data may be inaccurate.



Five of the cases studied here are classified under the heading of erythroblastosis fetalis. In two instances the clinical, laboratory, and pathologic data are conclusive. This includes the Rh information. Unfortunately Rh data is not available on two children but on clinical and pathologic grounds the diagnosis is quite certain. The fifth case probably falls into that group of patients with erythroblastosis where the Rh factor is not in question. The Rh typing of this patient and his parents was done early and may be incorrect. Several other cases classified elsewhere may have been erythroblastosis but no Rh data is available and the clinical findings are not complete enough to warrant placing them under this heading. Table III summarizes the findings of these five children. Sections of the liver are shown in Figs. 7 and 8.

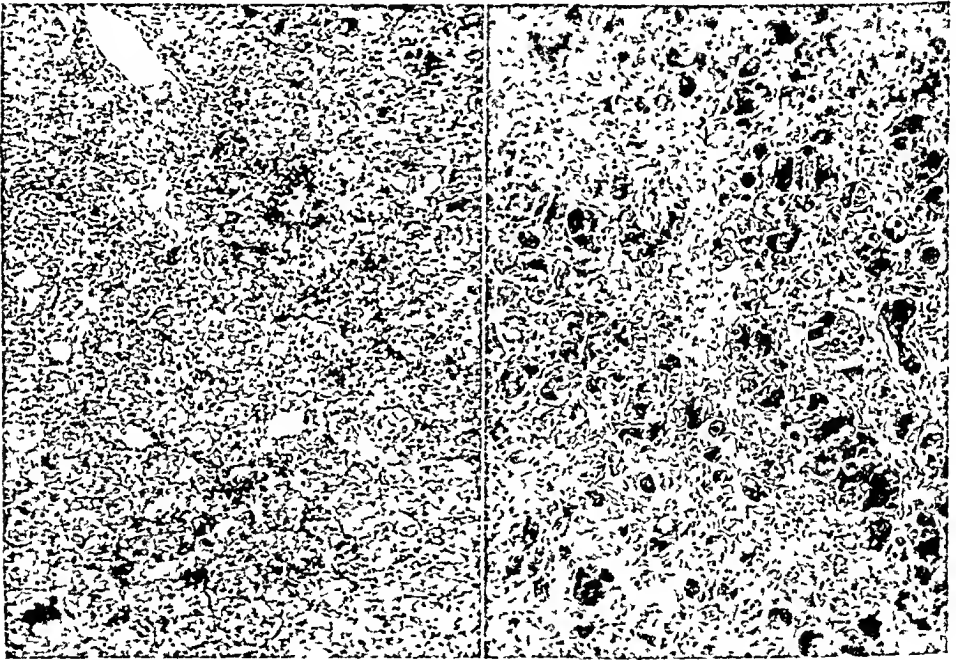


Fig. 7

Fig. 8

Fig. 7—J. E. Erythroblastosis, biopsy, nine days before death showing destruction of architecture, large, vacuolated, foamy, liver cells, diffuse hemorrhage, and old scar tissue with round cell infiltration. Regeneration of liver cells in some areas indicates actively progressive cirrhosis (Case 1, Table III) (Masson stain,  $\times 100$ .)

Fig. 8—J. E. Autopsy. Note increase in diffuse fibrosis and complete destruction of liver architecture. Generalized hemosiderosis (Masson stain,  $\times 100$ .)

The clinical findings in erythroblastosis fetalis include jaundice, edema or anemia. Such manifestations may occur at birth or soon thereafter. These manifestations vary with the gravity of the disease. Hepatomegaly and splenomegaly are prominent. Hemorrhagic manifestations may be present. Although some cases are rapidly fatal, most patients recover. Some of those who recover probably retain varying degrees of cirrhosis of the liver as

residuals. The presence of many nucleated red blood cells is the rule but is not universal. A leucemoid blood picture is usual. A high ieteric index is present. Low fractional proteins are often observed, and the prothrombin time frequently is abnormal. Of prime importance in establishing a diagnosis are the Rh data, which in 90 per cent of the patients will show an Rh-positive father and child but an Rh-negative mother. Agglutination antibodies in the maternal serum are conclusive evidence when they can be demonstrated.

A large spleen and liver with extramedullary hemopoiesis are usual but not universal findings at autopsy. Evidence of parenchymal damage to the liver usually can be demonstrated with hepatic necrosis and biliary stasis. Hemosiderosis usually is conspicuous. Whether cirrhosis occurs probably depends upon the extent and nature of the liver damage and whether or not the adverse situation of the liver is severe enough to prevent repair in the form of fibrosis. It would seem that the extremely severe cases would show progressive irreversible damage to the liver while the very mild cases would have no demonstrable changes. Between these two extremes some would show damage, destruction, and repair with some degree of fibrosis as the end result. In these cases the diffuse nature of the fibrosis, in contrast to the nodular distribution seen in other forms, has been a striking and consistent feature.

#### CONGESTIVE CIRRHOSIS

Congestive or cardiac cirrhosis is an entity quite different in clinical context and in pathologic picture from the other forms of cirrhosis. Some investigators feel that it should not be classified as true cirrhosis because it does not, to their satisfaction, meet all the requirements of the definition of cirrhosis by Moon.<sup>47</sup> "Cirrhosis of the liver occurs in several forms, is a progressive chronic inflammation, diffuse in extent, accompanied by fibrosis, retrogressive changes in the parenchymal cells and changes of remaining cells in the direction of proliferation." Regeneration is the feature that is usually hard to demonstrate in cirrhosis due to chronic passive congestion. Koletsky and Barnabee<sup>48</sup> studied seventy-five patients with heart disease in which prolonged single or multiple episodes of congestive failure had occurred. These they divided into three groups, of which the third showed not only atrophy, necrosis, and condensation of reticulum but "true cirrhosis," which included, with the other criteria, regeneration of hepatic tissue. They state: "The patchy nature of the fibrosis, and the intervening regions of central degeneration and condensation of reticulum made the picture differ considerably from that usually seen in advanced portal cirrhosis." They emphasize the distinction between single and multiple episode cases, and advance an ingenious concept of pathogenesis. It is presumed that gradual passive congestion leads to atrophy, rapid or terminal congestion, and to necrosis. In the intervals between episodes of gradual congestion recovery takes place with condensation and thickening of reticulum, but only if necrosis has spared enough of the lobule for healthy cells to replace the destroyed ones. Congestion severe enough to necrotize will not permit adenomatous regeneration. It must be realized that a special combination of circumstances must exist before a given cardiac patient will develop

TABLE IV. SUMMARY OF FINDINGS IN CONGENITAL CIRRHOSIS

CASE	AGE FIRST SYMPTOMS	AGE AT DEATH	DURATION OF INFANT DISEASE	EARLIEST SYMPTOM OF FAILURE OF LIVER	HYPERTROPHIC HEPATITIS	SPIRITNO-METAL	CLINICAL ASCITES	JAUNDICE	INFLECTIONS	PRINCIPAL CLINICAL AND PATHOLOGICAL DIAGNOSES
1	6 1/2 yr.	15 yr.	1 yr.	1 yr.	Palpable on first admission; not again until 5 yr. later, tender, firm; range 1-4 lb	1 yr, faintly palpable; 7 mo, 1 lb.	4 mo.	3 mo.	Pharyngitis, 4 yr., bronchitis, 3 yr., 2 yr., pneumococcal pneumonia, 2 mo.	Rheumatic heart disease with congestive failure; chorea; chronic endocarditis of all four valves with advanced mitral stenosis, fibrous pericarditis; lobar pneumonia; chronic passive congestion of liver with fibrosis and fatty degeneration.
2	12 yr.	1 1/2 yr.	Congenital	2 yr.	2 yr, to umbilicus, pulsating; at least one regression	2 yr, just palpable, 2 weeks, not felt	2 weeks, questionable.	No	2 yr., pneumonia, 2 1/2 mo., pleurisy.	Patent interventricular septum and foramen ovale, patent ductus arteriosus, infarcts of lung and myocardium, chronic passive congestion of lungs and liver, cirrhosis.
3	7 1/2 yr.	11 yr.	3 1/2 yr.	3 1/2 yr	3 yr., 1 2 lb; thereafter variable 0-4 lb.	No	3 mo.	No	3 1/2 yr., rheumatic fever.	Chronic rheumatic endocarditis involving mitral and tricuspid valves, fibrous pericarditis, chronic passive congestion of lungs, liver, spleen, and kidneys, cirrhosis, cholelithiasis.

4	7 yr.	9 yr.	Congenital	6 yr.	3 yr., 10 cm. below costal margin; variable thereafter.	3 yr., 1 lb.; palpation thereafter obscured by ascites.	2 yr., marked, progressive.	No	1 yr., erysipeloid; 1 yr., diarrhoea; 4 weeks diarrhoea; 2 yr., chronic otitis media	Congenital pulmonary valve stenosis, chronic passive congestion of liver and spleen, cirrhosis.
5	17 days	4 weeks	Congenital	9 days	17 days, 2 lb., firm.	17 days, 2 lb., firm.	150 c.c.	7 days, slight; 2 days, intense.	No	Saccular dilatation of patent ductus arteriosus; hypertrophy and dilatation of heart; thrombi in thebesian veins and in right and left ventricles, in abdominal aorta and several mesenteric branches; chronic passive congestion of liver, with marked loss of hepatic parenchyma, fibrosis, and calcification.
6	0½ mo.	7 mo.	-	-	2 weeks, hard, smooth, scalloped, 3-4 lb.	2 weeks, "enlarged."	2 wk. or more.	2 weeks, slight; terminally increased.	6 weeks, bronchitis.	Thrombophlebitis of hepatic vein near vena cava; cirrhosis; acute ulcerative colitis; chronic passive congestion of spleen and liver.

*lb* Represents "fingerbreadth below the costal margin."

*mo* Given represents interval before death.

\*Patient admitted with chlorea, the first clinical evidence of cardiac disease, compensated, was aged 11 years.

cirrhosis. Decompensation must be present intermittently to produce focal liver damage from chronic passive congestion and the interval repair by fibrosis of the damaged areas. Both clinically and pathologically, congestive cirrhosis resembles little the other forms of cirrhosis. Chronic passive congestion is the predominant features, as is brought out by Lambert and Allison.<sup>50</sup> Of course, heart disease per se with the common findings of chronic decompensation are the outstanding clinical features.

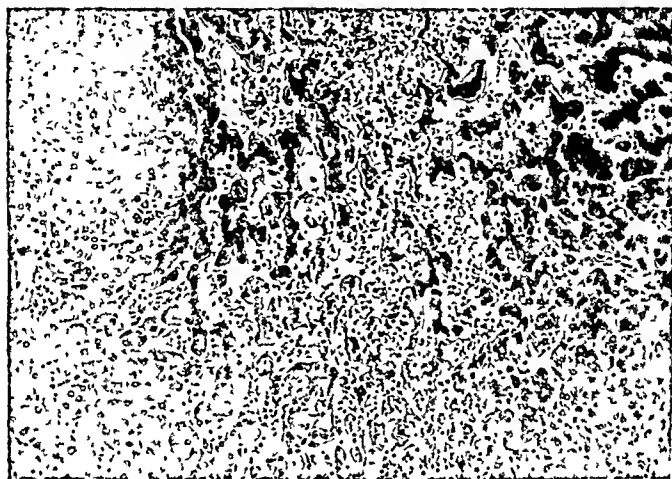


Fig. 9.—E W. Cardiac cirrhosis, showing dilatation of sinusoids in the region of the central vein, with atrophy of liver cells and some increase in fibrous tissue and reverse lobulation. (Case 3, Table IV.) (Masson stain,  $\times 100$ .)

On the status of cardiac cirrhosis as a clinical diagnosis it is worth while to quote Katzin, Waller, and Blumgart.<sup>51</sup> They studied 2,000 consecutive autopsies which included 286 cases of chronic passive congestion:

"By the evidence obtained the meaning of the term 'cardiac cirrhosis' is clarified. Cardiac cirrhosis (meaning morphologic increase in connective tissue in liver consequent to congestive failure) is present in the majority of patients who have suffered from even mild congestive failure for 9 months or more; the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, on the other hand (meaning extreme fibrosis which clearly results from chronic passive congestion and which causes evidence of portal obstruction), does occur, but is rare. Of the 286 cases of failure, there were only 15 in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure and particularly the presence of a palpable spleen. Not infrequently, however, the liver may be enlarged."<sup>51</sup>

Congestive cirrhosis may be viewed as the end result of prolonged but intermittent congestion of the liver. In children the usual cause is cardiac decompensation. However, one child whose case is presented here (Table IV) developed chronic passive congestion and cirrhosis of the liver because of an

obliterating endophlebitis of the hepatic vein with partial obstruction. Similar cases are reported in adults by Rigdon<sup>54</sup> and Hutehison and Simpson.<sup>55</sup> Zimmermann and Hillsman<sup>53</sup> were able to produce fibrosis in the liver experimentally by gradual occlusion of the vena cava. The clinical effects of cirrhosis on a congestive basis are likely to be overshadowed by the primary cause of the congestion in heart failure, but not so in patients where the obstruction to venous return is in the hepatic vein. The principal microscopic characteristic is an increase in central rather than in periportal fibrous tissue and necrosis of the liver parenchyma. Associated evidence of central chronic passive congestion (nutmeg liver) is striking. The only feature that seems to differ in children from the condition in adults is that the liver is more likely to be enlarged than shrunken.

Clinical and pathologic findings in this series of six cases are summarized in Table IV, and Fig. 9 shows a representative microscopic section.

#### POSTNECROTIC CIRRHOSIS

Postnecrotic cirrhosis is sometimes called coarsely nodular cirrhosis and healed acute or subacute yellow atrophy of the liver. It is a classification based principally on morphology, although sometimes the destructive or "toxic" agent can be identified. When it is identified the affection would be better classified under an etiologic category. This type of cirrhosis has been reproduced experimentally using different agents. Such experimental studies have contributed much to our understanding of the several diseases associated with cirrhosis. Among the common agents which are known to produce extensive liver necrosis which may result in subsequent scarring are chloroform, Salvarsan, einchophen, carbon tetrachloride, and the various sulfonamides (Moore<sup>16</sup>). The characteristic findings are a small liver with irregular liver nodules, interspersed with bands of scar tissue. The findings differ from those of nodular cirrhosis only in that the nodularity is much less regular and the parenchymal nodules are less uniform. Both gross and microscopic findings vary from case to case depending on the amount, the nature, and the time prior to exposure of the hepatotoxic agent. We agree with Karsner<sup>1</sup> that in many of the less classical cases one cannot distinguish between the two forms. The identification from the history of the etiological agent is desirable, when possible, to make the diagnosis more complete and certain.

Karsner<sup>1</sup> found the incidence of the postnecrotic type in his study to be 10 per cent (all ages), and he quotes several other writers whose figures are approximately the same. In our series only one definite instance among forty children was found. It is quite possible that some cases classified otherwise in the absence of a suggestive history might actually belong in this category.

The following is a brief history of one case:

J. L., a white boy aged 8 years, entered Children's Hospital in March, 1939. He was known to have ingested on several occasions in the previous month a total of at least twenty "Guaiasin" tablets, which contain the guaiacol ester of phenyl-einchonic acid, a chemical combination of einchophen and

guaiacol. During the two weeks before admission he had been well except for gradually progressive jaundice. The day before admission he became acutely and severely ill with high fever and delirium. Examination on admission revealed a well-developed, fairly well-nourished child who was febrile and comatose. A generalized icterus was very noticeable. The liver and spleen were not palpable. Laboratory studies showed the urine to contain hyalin and granular casts with occasional white blood cells. The white blood count was 13,000. The icterus index was 170, the nonprotein nitrogen 25 mg. per cent, the serum calcium 12 mg. per cent, and the phosphorus 2.5 mg. per cent. The clinical diagnosis was acute yellow atrophy of the liver. The patient rapidly became worse, his fever climbed, the coma deepened, and purpuric areas appeared on the lower abdomen and hands. Edema of the eyelids, face, and legs and ascites were noted on the day of death, which was the fourth after admission. A small 460 gram liver was found at autopsy. It was grossly nodular and firm in areas, but in other areas it was necrotic. The microscopic examination (Fig. 10) showed extensive cirrhosis with widespread focal necrosis. There was severe destruction of liver architecture. Most of the scar appeared to be old but unevenly dispersed throughout it were zones showing various stages of necrosis and repair, some with increased vascularization or with hemorrhage.

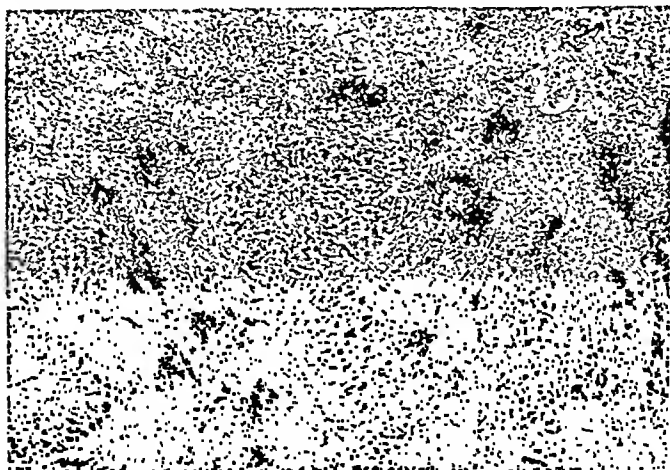


Fig. 10.—J. L. Cirrhosis due to cinchophen poisoning. The normal architecture is destroyed, so that more than one-half of the section shows scar tissue and focal areas of necrosis. Most of the scar appears to be old but dispersed unevenly throughout it are zones which show various stages of necrosis and repair, increased vascularity and hemorrhage. Liver cells are in isolated irregular nodules without a central vein. Section suggests repeated injury. (Masson stain,  $\times 60$ .)

In the light of the history it would appear that this liver had been subjected to more than one period in which a hepatotoxic substance had destroyed areas of liver parenchyma, whereupon necrotic zones were replaced by cirrhotic scar tissue.

The pathologic picture does not differ significantly from what would be expected in an adult with toxic (postnecrotic) cirrhosis.

Fig. 10 is a photographic reproduction of a representative area of this liver.

## HEPATOLENTICULAR DEGENERATION

An endeavor to survey comprehensively cirrhosis of all varieties will include mention of a small number of cases which have an equal or greater right to consideration among diseases of the central nervous system. These represent the condition to which Wilson<sup>56</sup> gave his name in 1912. What were probably the earliest two recorded cases were described by Gower in 1888 under the name of tetanoid chorea. Wilson<sup>56</sup> in 1912 attempted to absorb the "pseudosclerosis" of Alzheimer into his new syndrome. Two pathologic extremes exist between gross degeneration of the lenticular nuclei as described by Wilson and microscopic gliosis as described by Alzheimer. Hall<sup>57</sup> described a case with both, and gradations are now recognized under the term which he applied, hepatolenticular degeneration. A historical summary with references is given by Homburger and Kozol.<sup>58</sup>

The curious feature of the disease is the association of a degeneration in the brain, typically predominant in the lenticular nuclei but sometimes involving the cortex in lesser degree, with a marked but usually asymptomatic cirrhosis of the liver. The condition is rare. Strong<sup>59</sup> declares that a total of only fifty examples has been reported. Walsh<sup>60</sup> however, and Sweet, Gray, and Allen<sup>61</sup> suggest that it is not as unusual as has been supposed. Our finding of two proved and two possible cases in the files is in accord with this. Clinically<sup>59, 62</sup> the disease is characterized by insidious onset, usually in later childhood or young adult life. Although in its true form it is definitely heredofamilial in distribution, an essentially similar syndrome is encountered occasionally in acquired liver disease.<sup>63-66</sup> Bulbar palsy with dysarthria, hyperemotionalism, a progressive rigidity of the skeletal musculature, a coarse rhythmical tremor accentuated in emotional stress or in voluntary movements, and characteristic contractures of the hands, wrists, and feet are salient features. The mouth sags open with constant drooling and the facial expression is vacant or idiotic long before mental deterioration has reached a parallel degree. A zone of pigmentation at the limbus of the cornea, known as Kayser-Fleischer ring, is diagnostic when found. It is often missed without special examination. Loss of liver function may or may not be evident. Wilson stressed the silent nature of the inevitable cirrhosis but many authors<sup>60, 61, 67-70</sup> have since described cases in which evidence of liver disorder was present or even predominant.

CASE 1.—C. V. D., a white boy aged 12 years, was first seen in October, 1945. He had a family history that suggested that a sister had died at the age of 10 years from some sort of liver disease. Past history was negative. His present illness began two years prior to admission with bleeding tendencies. As time went on he developed stiffness of the joints and contractures of his hands. He was discovered to have a large spleen eight months before admission. A few weeks before entering the hospital he developed polydipsia and polyuria. Occipital headaches had been troublesome.

On examination the boy was listless, dull, and had great difficulty in enunciation. His sensorium was clear. He had numerous bruised areas. His



spleen was enlarged, firm, and not tender. The liver was enlarged. He had weakness in all extremities and his tendon reflexes were hyperactive. He had a urine of low specific gravity and a leucopenia. After discharge he developed progressive signs of basal ganglion disease and evidence of liver malfunction. A laparotomy was performed which disclosed a typical nodular cirrhosis of the liver. See Fig. 11 for the microscopic picture. The boy died a few hours after the laparotomy. A post-mortem examination was not granted.



Fig. 11.—C. D. Biopsy, hepatolenticular degeneration. Liver cells, among which is a scattering of pyknotic nuclei, are divided into islands by large smooth bands of connective tissue. Note absence of central vein. Some liver cells show pressure necrosis. (Hematoxylin-eosin stain,  $\times 60$ .)

CASE 2.—C. G., a white boy aged 14, was first seen in October, 1934. His brother had died at the age of 6 years from cirrhosis of the liver in another hospital. He gave a history of the steady development of the classical picture of Wilson's disease for a period of seven years. The physical findings in the liver were those of advanced portal cirrhosis. There was extensive softening of both lenticular nuclei.

Discussions of the etiology of this condition usually have concluded that the disorder in the central nervous system is secondary to that in the liver. The nature of the cirrhosis is indistinguishable from that in ordinary portal cirrhosis. Although the lesions of the brain are most prominent in the lenticular nuclei, they are not always confined to that area. Rabiner and associates<sup>70</sup> suggest that the vascular endothelium constitutes a blood-brain barrier serving to protect the brain from noxious agents, that this barrier may be a part of the reticuloendothelial system generally, and that disease of the liver or spleen might serve to break down this barrier and leave the central nervous system abnormally vulnerable.

The diagnosis of hepatolenticular degeneration cannot be made definite, in most cases, without finding both the characteristic neurologic manifestations and some evidence of hepatic cirrhosis. The strong heredofamilial nature

of the disease, however, may support a presumptive diagnosis when such a diagnosis already has been made in some other member of the family. The diagnostic Kayser-Fleischer ring should be looked for. Liver function tests may sometimes prove helpful in establishing the presence of liver dysfunction. Liver biopsy may be resorted to in selected instances.

#### UNCLASSIFIED JUVENILE CIRRHOSIS

Seven cases encountered in this study are not classified for lack of clinical data.<sup>6</sup> Because they did conform to the usual anatomical types they could not be placed under an anatomical classification.

Two of them presented the clinical and biopsy findings compatible with a diagnosis of obstructive biliary cirrhosis due to congenital anomaly of the bile ducts. However, at laparotomy the major extrahepatic bile ducts appeared to be patent. It is quite possible the site of obstruction was intrahepatic or in extrahepatic ducts that could not be visualized during the operation. One child died at home and the other in the hospital. An autopsy was not obtained on either.

Two additional patients who died early in infancy and who developed jaundice soon after birth were found at autopsy to have diffuse fibrosis of the liver. Both were febrile during their period of hospitalization. Cultures of *Bacillus coli* were grown from the blood of each patient. One had nucleated erythrocytes in the peripheral blood and extramedullary hematopoiesis in the liver, but this may have been due to the fact that she was premature. No Rh data were obtained. The possibility that bacterial invasion of the blood stream was the cause of liver damage is good but not conclusive. Many pathologists agree that bacteremia will, in selected cases, result in cirrhosis of the liver (Moon,<sup>71</sup> Karsner,<sup>1</sup> and Moore<sup>16</sup>).

In the fifth of these unclassified cases the patient was found at autopsy to have diffuse, moderate fibrosis of the liver. The patient was born a month prematurely and lived only two months. Evidence of erythropoiesis was obtained from the peripheral blood and the autopsy specimens. She also had a positive blood culture for *Staphylococcus aureus* which was believed to be the result of an abscess on her back. The clinical findings were not sufficient to make a diagnosis of erythroblastosis and no Rh data was obtained in those days. Perhaps the bacteremia was the principal etiological factor.

The sixth patient is a boy who at the age of 5 months was discovered to have a prominent splenomegaly and lymphadenopathy. At an outside hospital he is known to have been given multiple blood transfusions and sent home. He suffered from several intercurrent infections, including otitis media and pneumonia, before coming to Children's Hospital. Here a biopsy of a large liver was obtained that showed quite extensive portal and diffuse fibrosis. Skin and lymph node biopsies did not help make a diagnosis. Clinical impressions of xanthomatosis and agnogenic myeloid metaplasia were never substantiated. The clinical and pathologic classification of this child remain undecided.

The seventh patient, a white boy, had a brother die at the age of 5 months with "liver trouble." He was hospitalized at the age of 9 months with a history of jaundice for two months. He was undernourished and underdeveloped. A splenomegaly and hepatomegaly were found. Laparotomy disclosed a smooth liver. On microscopic examination mild, diffuse fibrosis was found. The etiology is obscure. The anatomic findings are not like those in the usual anatomic classifications.

These cases serve to emphasize that good clinical and laboratory data are essential to accomplish an accurate classification. Knowledge of the pathogenesis and etiology of cirrhosis is not as yet sufficient to make classification of cases easy, even when data is available. It would be a mistake to think of "juvenile cirrhosis" only in its classic nodular form.

#### THE DIAGNOSIS OF JUVENILE CIRRHOSIS

Many papers have appeared which discuss the symptomatology and diagnosis of cirrhosis. Most of them emphasize adult findings. A brief review of the peculiarities of the condition in childhood and infancy is undertaken here.

Enlargement of the liver even in advanced cases has been an almost universal finding. This is in contrast to the findings in adults where a small liver is the usual finding in advanced cirrhosis. Obstructive biliary cirrhosis in children is nearly always due to congenital atresia of the bile passages, while in adults this is never true. Cirrhosis as a sequelae to fetal erythroblastosis seems well established from this study while a relationship of the two conditions for adults is not established although admittedly possible. The occurrence of vascular spiders in the majority of adult patients has been emphasized by Bean<sup>72</sup> and by Patek, Post, and Victor.<sup>73</sup> In children with cirrhosis this physical finding is rare. A history of the ingestion of large quantities of alcohol for long periods of time is usual for people with adult nodular cirrhosis. Such a history is rarely encountered in children with the same variety of cirrhosis.

The importance of a careful clinical history cannot be overemphasized. The history of the ingestion of hepatotoxic agents that are powerful enough to cause cirrhosis is not likely to be elicited unless the interrogator has the possibility in mind. The cause of postnecrotic cirrhosis in the case reported in this paper was not suspected until autopsy. The patients with congestive cirrhosis with one exception (one with hepatic vein thrombosis) gave a history of prolonged and intermittent cardiac decompensation. The report of clay-colored stools since birth will always be available when the patient suffers from congenital atresia of the bile ducts, and it should be elicited. A history of syphilitic parents, of course, would cause immediate investigation of syphilis as the cause of symptoms in the newborn infant. To gain a knowledge of liver disease in other members of the family is imperative if such is the fact. It is important in evaluating suspected cases of cirrhosis to know about bleeding tendencies and of past episodes of jaundice. Data pertaining to the diet and development may be helpful in the study of, if not in the diagnosis of, juvenile cirrhosis.

Hepatomegaly, hepatomegaly with splenomegaly, jaundice, ascites, light-colored stools and dark urine are the common objective findings that draw attention to the liver as the site of disease. Prominent superficial abdominal veins, hemorrhoids, or other evidences of portal hypertension occasionally serve to focus attention on the liver.

Complete blood counts and routine urinalyses are essential in evaluating any case. The serology is essential to rule out syphilitic cirrhosis. Rh typing of the patient and parents should be accomplished to settle with a high degree of probability whether erythroblastosis is to be considered. Quantitative determination of Rh antibodies should be done if the clinical picture of erythroblastosis exists. In Negroes, careful and repeated search for the sickling tendency is indicated, because this form of anemia seems to be an occasional precursor of cirrhosis. Xanthomatosis usually shows characteristic changes in the skin or bones and if it or syphilis is suspected, skeletal films should be obtained. Liver function tests, if positive, will establish the presence of liver disease. They should always be obtained in suspected cases of cirrhosis not only as an aid in diagnosis but to help follow the progress of the disease. It is necessary to know when jaundice exists if it is obstructive, hemogenous, or hepatogenous. The required data to determine this, aside from the history, is history of bile in the stool, bile in the urine, or urobilinogen in the urine. The quantitative Van den Bergh also is helpful.

The diagnosis of obstructive biliary cirrhosis for all practical purposes in children depends on making a diagnosis of complete persistent obstructive jaundice. Once a diagnosis of congenital atresia of the bile ducts is established, one can conclude that obstructive biliary cirrhosis also exists. A history of jaundice from the time of birth or soon thereafter can be obtained. Clay- or white-colored stools from the time of birth is a universal finding. These babies are well nourished as a rule in spite of the jaundice. They often remain so for many weeks. Bleeding tendencies and evidences of portal obstruction develop late in the course of the child's short life. Jaundice and a high icterus index are prominent findings. Hepatomegaly, splenomegaly, and distention of the abdomen also are found. The laboratory findings substantiate the presence of an obstructive type of jaundice which in most cases is complete and persistent.

Nodular cirrhosis is usually an exclusion diagnosis. Most of the patients in this series had a clinical diagnosis of "Banti's disease," although some did not show the usual anemia or leucopenia. A history of bleeding tendencies, poor development, many infections, and an inadequate dietary intake may sometimes be obtained. Patek and Post<sup>80</sup> found the most common symptom to be insidious swelling of the abdomen. Two of the children whose cases are presented in this paper gave such a history. Jaundice often accompanies the terminal illness. The usual manifestations of Banti's syndrome are present. Evidence of portal hypertension is usually prominent. In the final analysis a liver biopsy is required to make a certain diagnosis because the diagnosis depends on the anatomic findings. The findings are not constant enough to make a certain clinical diagnosis.

The diagnosis of congestive cirrhosis depends on the establishment of a diagnosis of cardiac decompensation which has been chronic and intermittent. The physical findings, in addition to those attributable to heart disease, are those which indicate the presence of portal hypertension. Sometimes the hepatomegaly, splenomegaly, and ascites are the result of both chronic passive congestion from cardiac decompensation and the portal obstruction of cirrhosis. An evaluation of the role played by each is difficult. In most cases the cirrhosis can only be suspected because it does not always result even though cardiac decompensation has been present for a long time.

Postnecrotic cirrhosis should not be diagnosed clinically unless the findings of cirrhosis are found and a definite hepatotoxic agent can be identified. Sometimes it can be differentiated from nodular cirrhosis by experienced histopathologists on the finding of liver nodules that are more irregular in size and less uniform in pattern from those seen in nodular cirrhosis.

The diagnosis of cirrhosis as a part of the disease of erythroblastosis fetalis may be suspected clinically if evidence of portal hypertension develops. It probably will be a pathologic diagnosis in most instances until more serologically proved cases are followed and reported.

The diagnosis of hepatolenticular degeneration depends on finding both the characteristic neurological manifestations of the disease and in addition some evidence of hepatic damage. The diagnostic Kayser-Fleischer ring should be kept in mind. In advanced cases the physical and anatomic findings are identical to those of nodular cirrhosis.

#### SUMMARY

Forty proved cases of cirrhosis from the records of The St. Louis Children's Hospital, have been classified and discussed. Clinical and pathologic findings have been outlined and brief comparison made with the picture in adults.

Cirrhosis in children is rare, but not so rare as has been supposed. Defined as a diffuse fibrosis of the liver, it can be brought about in a variety of ways, some of which depend upon inheritance and some upon major derangement in some other organ system. The classification used here is etiologic in general; its limitations are those of the material at hand, which, although unusually large, is not representative of all known forms of the disease.

Obstructive biliary cirrhosis is due almost always to congenital anatomic anomaly. Clinically it is distinguished by an obstructive type of jaundice in the newborn infant and pathologically by interlobular fibrosis, bile stasis, and moderate inflammatory infiltration.

Nodular cirrhosis usually develops in childhood rather than in infancy, and is insidious in onset. Jaundice and hepatosplenomegaly are the most constant findings. The atrophic stage is rare. The liver shows extensive perilobular fibrosis, focal regeneration, and mononuclear cell infiltration without bile stasis.

Cirrhosis is a rare sequela of erythroblastosis fetalis. In addition to the usual clinical and pathologic findings of erythroblastosis there is diffuse fibrosis of the liver.

Congestive cirrhosis is the result of repeated severe passive congestion of the liver that alternates with periods of relative compensation. Clinically it is overshadowed by the primary disease of the heart. The excess fibrous tissue is central to the lobule rather than diffuse or peripheral. Hyperemia and dilatation of the sinusoids are typical. The liver is enlarged rather than shrunken. Hepatic vein thrombosis as a cause of congestive cirrhosis is rare.

A variety of toxins are capable of causing necrosis in the liver, which, if it is not too extensive, is followed by fibrotic repair. There seems to be nothing distinctive about this sequence as it occurs in children.

Two typical cases of hepatolenticular degeneration are described. So far as the liver is concerned they are indistinguishable from ordinary nodular cirrhosis.

The incompleteness of our understanding of this field is emphasized by the presentation of seven unclassified cases which illustrate the difficulties in exact diagnosis.

We wish to express our thanks to the professor of pathology, Dr. Robert Moore, for making available to us all data and material on those patients who came to autopsy.

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## THEPHORIN

### CLINICAL RESULTS IN ALLERGIC CHILDREN

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THE use of antihistaminic drugs in allergic diseases is based upon a theory which is yet to be conclusively proved. This theory postulates the liberation of histamine as a result of the union of the allergen and the sensitized cell in the shock organ. The resultant reaction supposedly produces histamine plus other physiochemical changes in the cell itself. Histamine liberation as a result of the allergic reaction cannot alone explain all the symptoms of allergy. Nevertheless, the recently introduced drugs which are able to neutralize the pharmacologic effects of histamine have proved themselves of great value in the relief of some allergic symptoms. The failure of these drugs to be universally effective only serves to emphasize again the inadequacy of the histamine theory as a complete explanation of the allergic reaction.

Benadryl and Pyribenzamine, the first antihistaminics produced in this country, have been followed by a plethora of many similar drugs evolved by pharmaceutical laboratories, each with claims of greater superiority and lesser percentage of side reactions. These compounds are phenolic ethers closely related structurally to Benadryl and Pyribenzamine.\* From the reports of others and from our own unpublished observations it is evident that they produce similar but varying percentages of side reactions. The most important side reactions encountered are drowsiness and sleepiness, which seem to occur with Benadryl more frequently than with most of the other compounds. In our previous study of Benadryl<sup>1</sup> numerous other side reactions were listed, and occur with most of these drugs. Their depressing effect is not always disadvantageous when treating allergic diseases in children, in whom their sedative action is often desirable, particularly in asthma and eczema.

In an effort to overcome the drowsiness produced by these drugs, cerebral stimulants such as dextro-amphetamine, desoxyephedrine, and caffeine have been used when indicated, especially in adults. A compound of Benadryl and Aminophyllin (Hydryllin-Searle) was found<sup>2</sup> to be superior to either Benadryl or Pyribenzamine from the standpoint of fewer and less severe side reactions. Aminophyllin exhibits an effective central nervous system stimulating effect in addition to its well-known ability to relax smooth muscle. This combination of

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From the Allergy Clinic, Children's Hospital of Michigan.

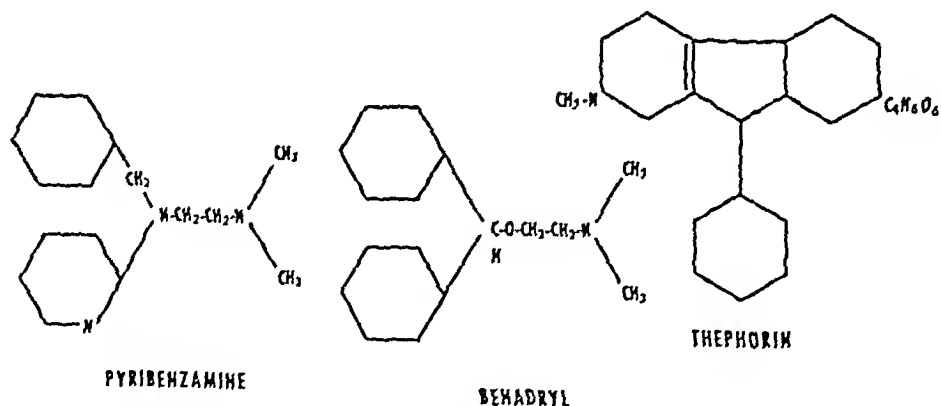
\*The following chemical compounds are similar in structure to Benadryl and Pyribenzamine, formulas of which are shown.

Antistine  
Decapryn  
Neo-Antergen  
Neo-Hetramine  
Histadyl  
Diatrin  
Trimeton  
Thenylene

Ciba  
Merrill  
Merek  
Wyeth  
Lilly  
Warner  
Schering  
Abbott

drugs produced a greater percentage of benefit not only in hay fever but also in noninfective asthma, in which patients the antihistaminics alone are far less effective.

Recently we have had the opportunity of studying an entirely new antihistaminic drug, characterized by a structure totally different from those previously reported, which, as pointed out, are all closely related. This drug is 2-methyl-9 phenyl-2,3,4,9-tetrahydro-1-pyridindine. The hydrogen tartrate salt is marketed under the name "Thephorin."<sup>10</sup> The structural formula of Thephorin is shown along with those of Benadryl and Pyribenzamine which are representatives of the older group of antihistaminics. Exhaustive *in vitro* and *in vivo* studies<sup>7-9</sup> have shown that this new drug is low in toxicity and high in antihistaminic effect. Pharmacologically the drug antagonizes the physiologic effect of histamine in experimental animals. It prevents histamine-induced contraction of the smooth muscles of the bronchi and intestines; it abolishes the effect of histamine on blood pressure and capillary permeability and is of value in preventing anaphylactic shock in the guinea pig. Acute toxicity studies in mice showed that it was about the same as Benadryl but only one-third to one-half as toxic as Pyribenzamine. There was no evidence of chronic toxicity.



Clinical studies with the drug by several previous observers<sup>7-9</sup> have been carried out almost exclusively on adult patients. These indicate a very high percentage of symptomatic relief, varying with different observers from 70 to 97 per cent in hay fever, 65 to 91 per cent in asthma and urticaria, and a significantly high percentage in allergic rhinitis and other allergic disorders. These observers reported that Thephorin produced fewer side reactions than other antihistaminics and caused drowsiness and sleepiness much less frequently than the older group of antihistaminics.

On the contrary, the majority of the side effects observed were due to its central nervous system stimulating effect, resembling similar effects produced by ephedrine and amphetamine. Our unpublished results<sup>10</sup> using Thephorin in 142 adults corroborates the observation of others that side reactions with this drug are slightly less frequent but much less severe than with other antihistaminics.

<sup>10</sup>Hoffman-LaRoche, Nutley, N. J.

In our series of adult patients, side reactions occurred in 30 per cent of the patients, but in only 8 per cent were they severe enough to warrant discontinuance of the drug. Clinical improvement occurred in 110 of 140 of our adult patients (77 per cent) treated for asthma, hay fever, allergic rhinitis, and urticaria.

The effect of the drug on allergic symptoms in children was presented in detail in one report.<sup>6</sup> Peters treated 142 patients, of which twelve were children 13 years of age or under. The results in all twelve children, some with hay fever others with asthma (pollen and nonpollen) were excellent. He reported no side reactions in this small group. Our preliminary study of this drug, begun in early 1948, was particularly stimulated by this remarkably favorable report of clinical relief with complete absence of side effects. A more extensive study of the drug in a larger group of children was therefore undertaken with great interest.

*Dosage.*—The drug is supplied in tablets of 25 mg. and in a syrup containing 10 mg. per teaspoon. Our case material consisted of patients seen both in the Allergy Clinic of the Children's Hospital of Michigan and in private practice. The dosage prescribed for younger children was one teaspoon of the syrup every three to twelve hours if necessary. Older children were given the tablets, 25 mg. every three to twelve hours as required, depending on symptoms.

*Results of Treatment.*—The effect of the drug was generally very definite. Relief was either marked and frequently complete or the drug was definitely ineffective. The mothers were usually quite certain as to the effect of the drug which, in the case of most of the children, was evaluated on objective symptoms. Relief, when produced, lasted from four to twelve hours. The effect of the drug was quite consistent in the same patient. This was in contradistinction to our previous experience with Benadryl, the effect of which was found to be variable in some patients at different times. In this series relief less than 50 per cent was noted as "no benefit."

TABLE I. THEPHORIN RESULTS IN ALLERGIC CHILDREN

DIAGNOSIS	PATIENTS	RELIEF OF SYMPTOMS				RELIEVED MORE THAN 50%	SIDE REACTIONS	
		100%	75%	50%	0 OR SLIGHT		PATIENTS	DISCONTINUED TREATMENT
Pollen H. F.	38	20	9	2	7	81%	10 = 26%	4 = 10%
Pollen asthma	12	6	2	0	4	75%	1 = 9%	0
and pre-asthmatic cough								
Perennial asthma	38	11	12	5	11	73%	8 = 20%	3 = 7%
noninfective								
Perennial allergic	9	3	2	1	3	66%	2 = 22%	1 = 11%
rhinitis								
Infantile eczema	4		3		1	75%		
Urticaria	8		4	3	1	87%		

*Hay Fever.*—Thirty-eight children having grass pollen or weed pollen hay fever were given the drug for symptomatic relief. Thirty-three (81 per cent) received 50 per cent or better relief. Many were receiving pollen desensitization and were given the drug for symptomatic relief on days when their symptoms were not under control. Others were new patients who received the drug in

an attempt to control symptoms while desensitization treatment was instituted. Even though some patients were thus receiving injection treatment, the action of the drug could be readily evaluated, since if relief occurred, it was usually prompt and definite within twenty to thirty minutes.

*Pollen Asthma.*—We treated twelve children with pollen asthma or pre-asthmatic cough. Eight (75 per cent) were relieved 50 per cent or more.

*Perennial Asthma.*—We treated thirty-eight children whose asthma was perennial in nature and noninfective in type. Twenty-eight (73 per cent) received very definite clinical benefit. These results are much better than with many of the other antihistaminics that we have used. Asthma complicated by respiratory infection responds poorly to Thephorin. We have made the same observation with many other antihistaminic drugs.

*Perennial Allergic Rhinitis.*—Nine children were treated with the drug, of whom six (66 per cent) were benefited 50 per cent or better.

*Infantile Eczema.*—Only four infants were available for trial with the drug. In three of these (75 per cent) there was definite relief of itching.

*Urticaria.*—In eight cases of urticaria in young children seven were very appreciably relieved by Thephorin. None of these were chronic cases, and it would be difficult to attribute the improvement in such cases to the drug alone. Acute cases of urticaria are well known to be of short duration. However, the drug was very definitely of benefit in reducing the itching.

We also used the drug in several children for the prevention of reactions following pollen injections. In four children in whom the drug was so used the tendency to such reactions was greatly reduced.

*Side Effects.*—Side reactions occurred as follows in our 109 patients:

Slight drowsiness	13
Severe drowsiness	2
Epigastric pain and/or nausea	4
Constipation	1
Restlessness and excitation	2
Total	22 patients

We were thus unable to confirm Peter's observation in regard to the complete absence of side reactions in children. In our 109 patients there were 22 (21 per cent) side reactions. However, only nine (8 per cent) were severe enough to discontinue the drug.

In fifteen of the twenty-two children in whom side reactions occurred, drowsiness was the chief symptom. This in contrast to the observations of others and ourselves in regard to the side reactions to Thephorin in adults. In the older patients a sedative effect from Thephorin is seen much less frequently. The chief side reactions in adults consist of central nervous system stimulation and gastrointestinal symptoms.

It is apparent that Thephorin is an effective antihistaminic drug and a valuable addition to the measures available for the palliative treatment of allergic diseases in children.

Such new drugs in no way lessen the importance of adequate studies and subsequent specific treatment when indicated in these conditions.

## SUMMARY

1. Thephorin, a new antihistaminic drug, differing structurally from previous evolved antihistaminics, has been evaluated clinically in 109 allergic children.

2. It was found to be very effective for symptomatic relief as follows:

Hay fever	81% relieved
Pollen asthma	75% relieved
Perennial asthma	73% relieved
Allergic rhinitis	66% relieved
Infantile eczema and urticaria	75% relieved

3. Thephorin produced side reactions in 20 per cent of this series. Reactions were seldom severe enough (8 per cent) to discontinue use of the drug. Thephorin has a mild sedative effect in children in contrast to the stimulating effect seen in adult patients.

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## A CORRECTION

In the February issue of *THE JOURNAL* a case report was published entitled "Hyeodan (Dihydrocodeinone) Poisoning" which title may have been misleading. It was not in any way the intention of the authors to create the impression that they have found Hyeodan, in therapeutic doses, to be toxic. The authors wish to make clear that the article dealt with a single case of an unusually large overdose of Hyeodan taken by an unguarded 3-year-old child—in fact forty times the recommended dose. The purpose of the article was to report the measures taken which brought about a complete recovery within a few days. The authors feel that perhaps a more responsive title for the article would have been: "An Accidental Case of Poisoning Following a Large Overdose of Hyeodan—With Complete Recovery."

(Signed) Henry Raseoff, M.D.  
March 31, 1949.

## Case Reports

### COOLEY'S ERYTHROBLASTIC ANEMIA IN A NEGRO GIRL

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**E**RYTHROBLASTIC anemia as originally described by Cooley<sup>1</sup> is a progressive disease characterized by certain typical clinical features and changes in the hematologic picture and osseous system. Physical observations include pallor, underdevelopment, a large head with a Mongoloid face, flattened nasal bridge, prominent cheek bones, cardiac hypertrophy, hepatomegaly, and extreme splenomegaly.

The blood shows leucocytosis, severe hypochromic anemia, many erythroblasts, reticulocytosis, and decreased red cell fragility.

The distribution of bone changes in this clinical entity is generalized over the entire skeleton. The roentgenographic characteristics of the disease are widening and increased transparency of the long bones with thinning of cortices due to pressure from hyperplastic bone marrow. Medullary trabeculae are prominent. The skull shows thinning of the inner and outer tables. The outline of the outer table may be obliterated owing to atrophy from pressure by thickened diploe. The cancellous diploic bone is thickened, and closely packed striations resembling fine bony spicules situated perpendicular to the outer table in radial patterns are seen. The skull vault is thickened due to hyperplastic, hematopoietic components of the diploe.<sup>2-5</sup>

Cooley<sup>6</sup> and others who have investigated this anemia have not held the opinion that it is race-limited, although the disease is familial. Studies of Italian families by Dameshek<sup>7</sup> have revealed cases ranging in severity from Cooley's erythroblastic anemia to cases with mild hypochromic anemia, target-oval and stippled cells, and decreased red cell fragility. These syndromes, inherited as a simple mendelian dominant, showed a high incidence of transmission in the offspring. Valentine and Neel<sup>8</sup> conducted a genetic study which favored the hypothesis that the mild state is due to heterozygosity for a factor which, when homozygous, results in a full-blown erythroblastic anemia.

There have been several authentic cases of erythroblastic anemia reported in races other than the Mediterranean group. These include a case in an English child,<sup>9</sup> three cases in Chinese,<sup>10, 11</sup> and one in an Indian boy.<sup>12</sup> Dameshek<sup>7</sup> mentions one case occurring in a Negro boy seen at the Mt. Sinai Hospital in New York. Two other cases in Negroes have been reported, one by Stiles,<sup>13</sup> another by Faber.<sup>14</sup>

The prognosis of Cooley's anemia is unfavorable and treatment is unsatisfactory. One has to rely on blood transfusions to keep the hemoglobin above the critical level of 5 Gm. per cent. Good effect from splenectomy on identical Greek twins was observed by Govan.<sup>15</sup> Following the procedure, they required only one-third to one-fifth as much blood to maintain their hemoglobin above a critical level, and their general condition improved. However, the apparent results from these cases would not seem to justify it as a routine procedure. Blackfan and Diamond<sup>16</sup> state that splenectomy is contraindicated as it has not been followed by retardation in the progress of the disease, and suggest that the anemia may progress more rapidly.

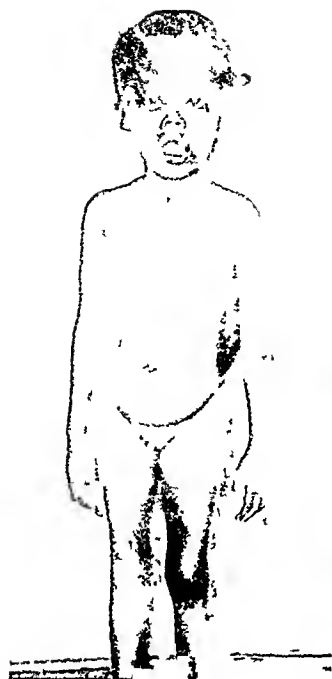


Fig 1



Fig 2.

Fig 1—Front view of patient, showing palpable extent of spleen and liver.

Fig 2—Direct posterior-anterior view of the chest. Moderate enlargement of the heart generalized in all diameters, is seen with lung fields showing no definite evidence of pulmonary edema. Ribs and shoulder girdle show increased extent and prominence of trabeculation of marrow cavities, and thinning of cortex.



Fig 3—Inset of Fig 2, showing bone changes in greater detail

## REPORT OF CASE

M. L. R., a 6-year-old Negro girl, was referred to the hospital on April 19, 1948, by Dr. W. B. Worley. She had had a cold with cough and chest pain for a month. The mother stated that she had a poor appetite and had been thin all her life. She had been in this hospital on Sept. 25, 1945, for a fractured humerus, and again in March, 1947, for bronchopneumonia. At that time she was found to have a severe anemia, but studies were inadequate to classify it. However, numerous nucleated red cells were observed in blood smears and she was given 750 c.c. of blood in three divided doses. The mother, father, and four siblings were living and well.

Physical examination on April 19, 1948, revealed an undernourished, pale, Negro girl not acutely ill. Her head was large, especially in the parietal regions, and she had a Mongoloid face (See Fig. 1). Blood pressure was 104/80. There was a systolic murmur over the entire precordium and the heart was enlarged to the left. The liver and spleen were both enlarged, being palpable 5 cm. below the costal margins. There were no other significant physical findings.

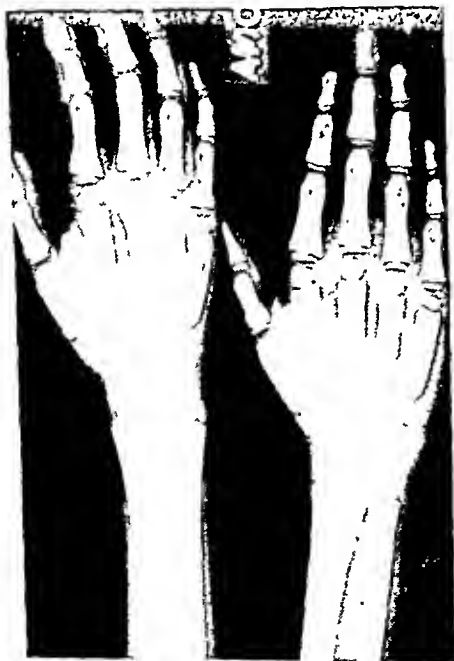


Fig. 4.—Views of both hands and wrists. The marked increase in extent and prominence of trabeculations in medullary portions of bones, is seen, with marked, uniform thinning of cortex surfaces. Only three carpal bones are ossified, suggestive of retarded maturity for chronological age.

The blood count showed 1.8 Gm. hemoglobin, 850,000 red cells, 15,650 leucocytes with 64 segmented neutrophils, 19 stabs, 1 juvenile, 15 lymphocytes, and 1 monocyte. There were 507 nucleated red cells per 100 white cells. The red cells showed marked poikilocytosis, anisocytosis, hypochromia, and polychromatophilia, with many target cells (See Fig. 6) and many Howell-Jolly bodies, stippled red cells, and Cabot's rings. The sickling test was negative on four occasions. Platelet count was 250,000, reticulocyte count 5.4 per cent. The erythrocytic fragility test was reported as follows: hemolysis on patient begins at 0.34 and is not complete at 0.28. Hemolysis on control begins at 0.42 and is complete at 0.30. Icteric index was 14.4.



Smears of sternal marrow showed marked hyperplasia of erythroid elements, the myeloid/erythroid ratio being 1/20.

Results of x-ray films made on this patient were reported as follows:

"Skull: There was marked thickening of the diploe throughout the entire extent of the calvarium, with striations situated in a radial pattern.

"The hands showed swollen appearance of tubular bones, with cortices thinned and increased prominence of trabeculae of the medullary cavities. Only three carpal bones were present, suggestive that bone maturity may be slightly



Fig. 5.—Skull, showing thinning of the tables, with marked hyperplasia and thickening of the diploe. The radiate striations perpendicular to the diploe are suggestive of advanced hyperplasia of hematopoietic elements.



Fig. 6.—Smear of peripheral blood showing erythroblasts, hypochromic, macrocytic erythrocytes, and target cells.

retarded. The chest showed moderate, generalized enlargement of the heart in all diameters. Lung fields appeared clear. In all the bones of the thoracic cage and shoulder girdle, were seen marked thinning of bone cortices and increase in prominence of the trabeculae of the medullary cavities.

"Similar changes were seen in spine, pelvis, and lower extremities.

"Impressions: Advanced hemolytic anemia, type undetermined, the type of which requires the following differential diagnosis; (1) Cooley's Mediterranean anemia; (2) sickle cell anemia; and (3) familial hemolytic (spherocytic) anemia."

Treatment of this patient has consisted simply of repeated transfusions in approximately 200 c.c. doses. After receiving 1,000 c.c. of whole blood over a six-week period, her hemoglobin was 8.5 Gm., red blood cells 2,930,000.

She showed considerable improvement on this treatment and was discharged to return at monthly intervals for examination and transfusions.

#### SUMMARY

1. A review of the literature on Cooley's erythroblastic anemia is given.
2. A case occurring in a Negro child is reported to illustrate further that the disease is not limited to individuals of Mediterranean origin.

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# CONGENITAL CYSTIC DISEASE OF LUNG IN INFANCY

## REPORT OF A CASE WITH NECROPSY FINDINGS

GEORGE A. McCLOSKEY, M.D., AND MAUD L. MENTEN, M.D.  
PITTSBURGH, PA.

CONGENITAL cystic disease of the lung is not common at any age and rarely is diagnosed in infancy unless the condition has given rise to symptoms. The condition in recent years often has been treated surgically. The case to be presented is of a male baby who showed, shortly after birth, a sternal retraction which progressed in a few weeks to the development of a funnel type of chest. This chest deformity was brought about by a polycystic condition of the upper lobe of the left lung. The death of the child occurred at 6 weeks of age and the clinical history and autopsy findings are presented herein.

The earliest report of cystic disease of the lung was by Bartholinus<sup>1</sup> in 1687. The first real contribution to the literature of this pulmonary condition was in 1925 when Koontz<sup>2</sup> collected 108 cases from the literature, 26 of which occurred in the first ten years of life, and of these, sixteen were in the first year. Later, many papers appeared describing individual cases. By 1937, Wood and associates<sup>3-7</sup> had added forty-eight surgically treated cases. In the same year, Schenck<sup>8, 9</sup> collected a total of 381 cases from the literature. Up to the present time, additional single case reports have brought the total to about 450.

## REPORT OF A CASE

L. D. M., a 6-week-old male infant with a history of dyspnea, cyanosis, and difficult passage of stools of five weeks' duration, was admitted to the Children's Hospital of Pittsburgh on May 4, 1948, to the service of Dr. E. R. McCluskey. There were no episodes of upper respiratory infection. On admission the infant appeared malnourished, underdeveloped, and in moderate respiratory distress with cyanosis except when at rest. The temperature was 98.6° F., pulse 126, and respirations 26.

The thorax had a funnel type deformity and a large left hemithorax. Infra-sternal, intercostal, and a slight suprasternal retraction were marked on inspiration. The trachea was shifted well to the right. The mediastinum was also displaced to the right and the apex beat of the heart could be palpated at the left sternal border. Resonance over the left chest was almost tympanic, while the right chest was hyporesonant except for a dullness over the site of the heart. Breath sounds were distant over the left chest, absent over most of the anterior right chest, and bronchial over the left lateral and posterior chest areas. The abdominal wall was flabby and possessed little muscular tone. Bilateral indirect inguinal hernias were present. The remainder of the physical examination was essentially negative.

The laboratory results showed an essentially normal urine. Blood examination showed a hemoglobin of 9.4 Gm., red blood cell count of 3,200,000, and a white blood cell count of 13,600 with 56 per cent granulocytes and 44 per cent lymphocytes.

Röntgenogram examination of chest showed normal bone contours except for a marked indentation at the base of the sternum (Fig. 1). The heart, mediastinal structures, and trachea were displaced into the right lung field, with

From the Departments of Pathology and Pediatrics, University of Pittsburgh and Children's Hospital of Pittsburgh.



Fig. 1.—Roentgenogram showing deformity of sternum and emphysema of the left upper lobe of lung.

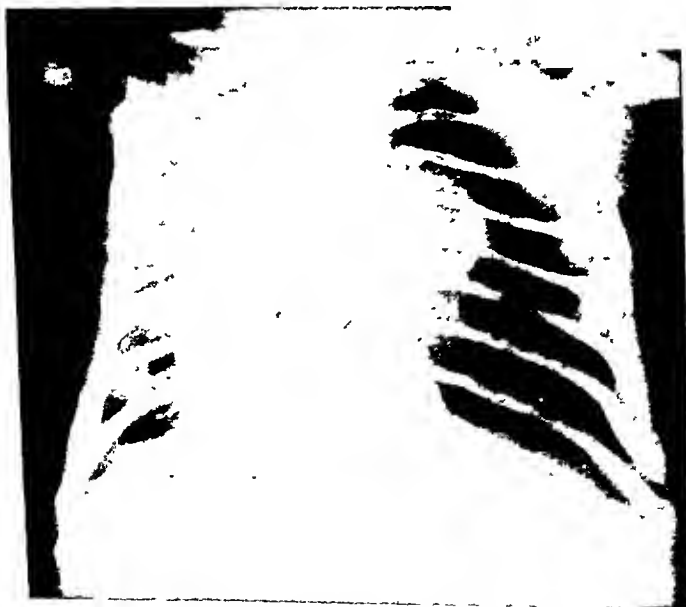


Fig. 2.—Roentgenogram showing cyst in left hilar region and emphysema of left lung field with displacement of heart and mediastinum to the right.

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Fig. 1.—Roentgenogram showing deformity of sternum and emphysema of the left upper lobe of lung.



Fig. 2.—Roentgenogram showing cyst in left hilar region and emphysema of left lung field with displacement of heart and mediastinum to the right.

the right border of the heart almost approximating the right lateral chest wall. In the left hilar region there was a round opacity suggestive of a cystic structure which measured 2.5 cm. in diameter (Fig. 2). The left lung field was emphysematous with the exception of a small area of increased density immediately caudad to the area of left hilar opacity. The impression was that of a left hilar cyst with emphysema of the upper and lower lobes of the left lung.

Bronchoscopic examination demonstrated a trachea deviated to the right, clear right and left main stem bronchi, and a smaller than normal left main bronchial orifice which did not permit passing of the bronchoscope.

The course of the patient was downhill with progressively increasing air hunger, dyspnea, cyanosis and rapid pulse. Temperature elevation was never over 100° F. The respirations ceased on the seventh hospital day.



Fig 3—Gross specimen revealing an emphysematous left upper lobe with an attached accessory lobe and a compressed left lower lobe. The right lung shows marked compression with peripheral emphysema.

The necropsy was performed two hours after death. The body was that of an emaciated, poorly developed, white male child measuring 55 cm. in length. Bilateral indirect inguinal hernias were present. There was an enlarged left hemithorax. Examination of the neck and upper thorax revealed the trachea deviated to the right. The lower end of the sternum showed a concavity involving its inner surface. The abdominal muscles were of poor tone. The mediastinum together with the left lung were markedly shifted to the right and the right lung was compressed to a smaller size than normal. The left lung, measuring 11 by 8 by 5 cm., showed an anomalous lobation. It consisted of the two main lobes, upper and lower, and a small accessory lobe partially separated from the upper lobe (Fig 3). The upper lobe filled a large part of the left thorax and its median border was located 3 cm. to the right of the midline. On sectioning, the ant surface of the upper two-thirds of this lobe showed numerous cysts of varying size. The cysts varied from 2 mm. to 25 mm. in diameter

(Fig. 4). The largest of these cysts, measuring 2.5 by 2 cm., extended outward from the hilus and occupied one-third of the inner part of the lobe (Fig. 4). This cyst lay directly over the main bronchus supplying the upper lobe. The cavity contained yellowish gelatinous mucus and had a thickened, corrugated surface which in two or three places communicated with adjacent underlying bronchi. The lower one-third of the cut surface of this lobe appeared emphysematous. The bronchus supplying the left upper lobe was patent and measured about 4 mm. at its origin and about 2 mm. at the middle of the lobe. The lower lobe, measuring 5 by 3 by 3 cm., was small and was displaced by the excessively expanded upper lobe into a position posterior to and left of the heart. It had a dark reddish color, was firm, and possessed little air-holding tissue. This lobe on section appeared firm but not consolidated and was supplied by a bronchus which measured 3 mm. in diameter at its origin on the medial surface. The accessory lobe (Fig. 3), measuring 4.5 by 3.5 by 1 cm., was attached for 1.5 cm.



Fig 4 —Section of cut surface of left upper lobe showing hilar cyst with cystic dilatation and emphysema of surrounding pulmonary tissue

at the hilar surface to the left upper lobe. Its free border was divided into three irregular scallops. It was dark reddish blue in color and firm. On section, the tissue appeared solid and not air-holding. This lobe was supplied by a branch of the bronchus to the upper lobe which was about 2 mm. in diameter at its origin.

The right lung measured 9.5 by 6 by 4 cm. and showed a normal lobation except for an incomplete separation of the middle from the upper right lobe. With the exception of an emphysematous, pinkish-white area at the periphery of the lateral surface of the middle lobe, this lung showed moderate expansion



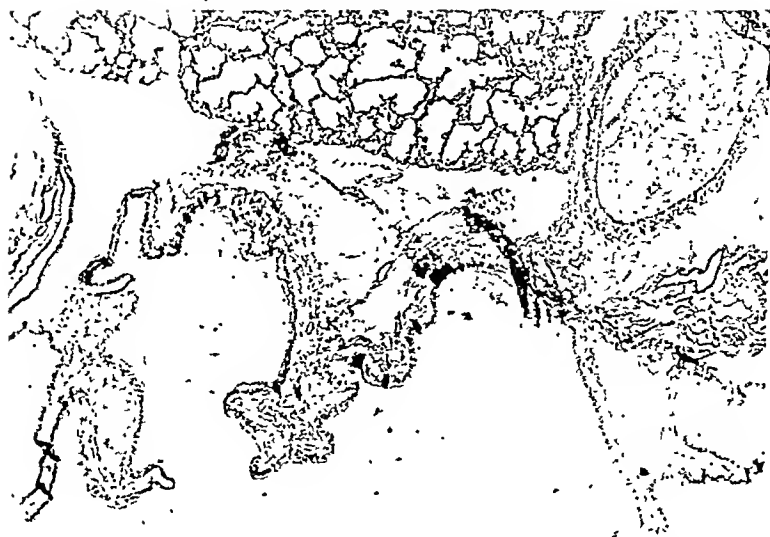


Fig. 5.—Cross section of upper lobe of left lung showing papillary projection of cyst wall. (Hematoxylin and eosin stain,  $\times 30$ .)

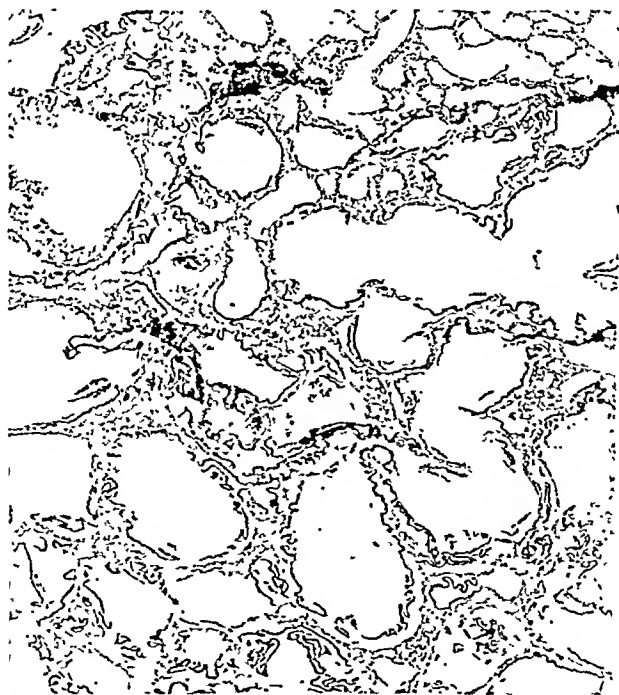


Fig. 6.—Cross section of upper lobe of left lung showing dilated terminal bronchioles, respiratory bronchioles, and acini. (Hematoxylin and eosin stain,  $\times 30$ .)

and appeared firm and reddish in color. On section the organ appeared somewhat more solid than normal, but fairly air-holding. The other findings were essentially normal.

*Anatomic Diagnoses.*—Diagnosis was cystic disease of upper left lobe of lung; funnel-shaped deformity of chest; shifting of mediastinum to right; acute dilatation of right heart; emphysema; partial atelectasis of the lower lobe of left lung and of the right lung; bilateral inguinal hernias.

Sections were examined from all parts of both lungs. Microscopically, these fell into two groups: (1) polycystic in type, and (2) possessing architecture of normal lung with superimposed lesions of primary atypical pneumonia of unknown etiology.

In Group 1 the pleura was normal. The cystic dilatation was primarily in the bronchial tree and pronounced in the terminal bronchi and respiratory bronchioles (Fig. 5). The bronchi had a somewhat hypertrophied epithelium which stained deeply and in some areas was desquamated. A few of the larger bronchi contained a pink staining mucus. The alveoli which remained intact were relatively few in number and markedly dilated. The lining of the large cyst consisted of villuslike projections of bronchial wall with a thick connective tissue core covered with high columnar epithelium having prominent cilia. In the depressions between the bases of the papillary outpouchings, adherent pink mucoid masses were observed. The adjacent lung tissue showed dilated respiratory bronchioles and a few dilated alveoli. It was difficult to differentiate respiratory bronchioles, small terminal bronchioles, and alveoli because the majority of the dilated spaces were ballooned to many times their normal size (Fig. 6). The remainder of the lung showed a normal architecture upon which was superimposed a primary atypical pneumonia; the alveolar walls were thickened by an infiltration of round cells which had materially reduced the alveolar spaces. In some areas a compression atelectasis was present. The alveoli contained desquamated, hypertrophied, lining epithelial cells and erythrocytes. The other organs appeared essentially normal.

#### DISCUSSION

In our patient the abnormalities of chest referable to alterations in pulmonary structure were present at birth; consequently, the condition may be classed as congenital cystic disease regardless of the mode of pathogenesis. Various theories which have been enumerated by Müller<sup>10</sup> and by King and Harris<sup>11</sup> have been suggested for the origin of congenital cystic disease of the lung. One of the theories which has been widely accepted is a lack of canalization in small areas of the solid, cellular bronchioles present in the early developing lung. It is probable, however, that such factors as infection, anomalous lobation, and blood supply also play a considerable role in the formation of pulmonary cysts. When a bronchiole becomes occluded, expansion may occur above and below the block either because of increased air pressure or accumulation of mucoid secretion, so that primary cyst formation is usually associated with emphysema of the contiguous lung. This latter condition was brought about in our case by pressure of the large cyst on the main bronchus of the upper left lobe. The communications which existed between the large cyst and other adjacent bronchioles did not materially relieve the intra-cystic pressure because of the retained mucus.

All cysts of appreciable size are lined with papillary projections of bronchial epithelium, which feature was prominent in our case. It is readily understandable how symptoms of dyspnea can occur by obstruction in the lung. In those patients in which pressure is exerted on the heart, cyanosis may also be a symptom.

The differential diagnosis may implicate almost any pulmonary disease, e.g., acute infections, neoplasm, localized empyema, tuberculosis, hydatid cysts, and diaphragmatic hernias. The diagnosis in our patient was fairly obvious from x-ray films, but the sudden death of the child, probably from the associated viral pneumonia, occurred before surgical intervention could be consummated.

#### SUMMARY

Cystic disease of left lung, in an infant dying at 6 weeks of age, resulted in deformity of the sternum and displacement of the mediastinum, heart and left lung to the right. Necropsy revealed an associated primary atypical pneumonia of undetermined origin.

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# TETANUS OF THE NEWBORN INFANT

## REPORT OF A CASE WITH RECOVERY

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CEDAR RAPIDS, IOWA

**T**ETANUS neonatorum, which carries a very high mortality rate, has fortunately become a rather rare disease in this country. Cases of recovery, therefore, seem worthy of reporting.

### CASE REPORT

On Aug. 30, 1948, a normal female baby was delivered spontaneously at a farmhouse. The birth weight was 6 pounds. The umbilical cord was tied by the attending physician with the usual umbilical tape (cloth). The navel was kept covered with a navel band. The cord came off on the fifth day and the stump looked clean; on the ninth day it appeared well healed. On the tenth day the baby became irritable but took the bottle well. The same evening she vomited once. On the eleventh day the parents noted that the baby held her fists tightly clenched and seemed to "make grimaces." They also thought the baby was unusually "strong," misinterpreting beginning rigidity as muscular strength. By the thirteenth day the baby was very fussy and had "spells" of clenching her fists. A drop of blood was noted on the navel. Profuse perspiration of the forehead and spells of "straightening out" frightened the parents. The temperature was 100° F. rectally. The baby continued to take the bottle fairly well but vomited on occasions. In the afternoon of that day, the mother heard the baby "panting terribly fast." She found the baby covered with perspiration and rather "stiff." The temperature was 106.2° F. rectally. The baby was taken to the hospital; during the trip she suffered three spells of "doubling up."

*Course in Hospital.*—On admission, the outstanding symptom was a marked, generalized rigidity. The following findings, present only in part when the baby was first seen, became more pronounced and typical of tetanus on the second and third day of hospitalization: The forehead was wrinkled, there was a risus sardonius, the neck muscles were taught, and there was opisthotonus. The abdominal wall was boardlike; the extremities were hyperextended. The fists were tightly clenched and the toes spread out in fanlike fashion. The baby could be lifted up from the crib like a "wooden doll." She weighed 5 pounds, 4 ounces.

Three diagnostic possibilities were considered: tetany of the newborn, intracranial hemorrhage, and last, because of its rarity, tetanus neonatorum. Blood was drawn from the femoral vein for a calcium determination and 10 c.c. of calcium gluconate were injected. This did not produce any relaxation. The calcium value was 11 mg. per 100 c.c. A lumbar puncture was unsuccessfully attempted. Repeated the next morning, it yielded xanthochromic fluid under normal pressure, containing 1,200 red blood cells per cubic millimeter and no leucocytes. In retrospect, it was, of course, realized that the blood in the spinal fluid was traumatic. Bilateral subdural taps failed to reveal any bloody fluid. By now, symptoms typical of tetanus had become so pronounced that there was no more doubt about the diagnosis. 10,000 units of tetanus antitoxin were injected intramuscularly; this was repeated the following day. Chloral hydrate,

From the Department of Pediatrics, St. Luke's Hospital.

5 gr., was administered in oil per rectum every four hours; 1 c.c. of magnesium sulfate in 50 per cent solution was injected intramuscularly every six hours. Sodium phenobarbital, in doses of  $\frac{1}{8}$  to  $\frac{1}{4}$  gr., was given hypodermically as necessary to supplement the effect of those drugs. Penicillin, 10,000 units, was given intramuscularly every three hours.

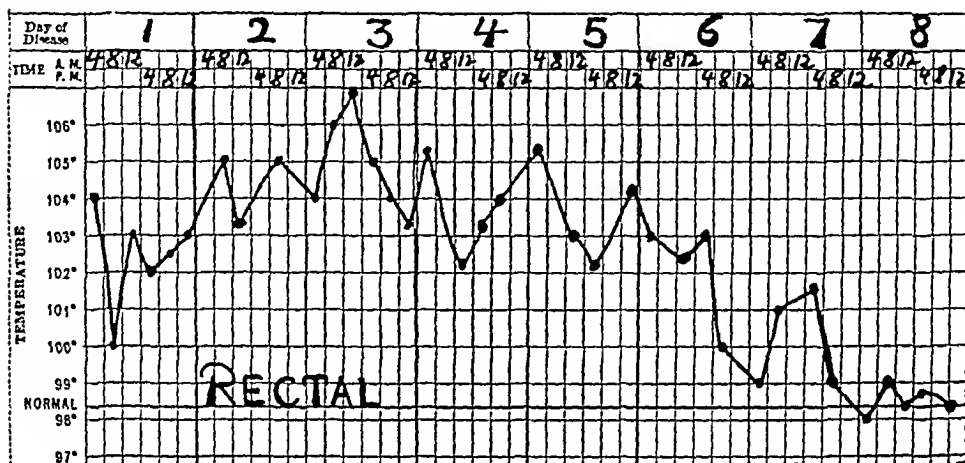


Chart I.

For the next twenty days the clinical picture was dominated by nearly constant rigidity which did not even leave the baby entirely when she slept. The slightest disturbance would produce "tremors" and increase in tonicities. The temperature is recorded in Chart I. Feeding at first was by nasal gavage but much of the formula (even when thickened with Pabulum) was regurgitated. On the sixth hospital day the baby nursed fairly well from the bottle, but regurgitation persisted. By the tenth day, she took 2 ounces of a skimmed milk formula with Dryco and dextrose. The fluid intake was supplemented by subcutaneous injections of 5 per cent glucose in water and normal saline. On the eleventh day stools containing mucus were noted. It was believed that this may have been due to the continuous rectal administration of chloral hydrate. The drug was stopped and replaced by phenobarbital sodium. Feedings were replaced by boiled water only. Whole blood, Amigen, and electrolytes were given intramedullary into the tibiae. On the fourteenth day the injections of magnesium sulfate were discontinued, after a slough had developed on one of the buttocks. By the fifteenth day severe diarrhea was present. The baby became considerably dehydrated. Blood, plasma (from the hospital's blood bank) and electrolytes were given intravenously, intramedullary, and (twice) intraperitoneally (glucose and saline only). The diarrhea lasted about ten days, then subsided. In the meantime, the baby's rigidity had greatly improved. By the sixth week recovery was steadily progressing; the baby was relaxed and gaining well. However, she continued to keep her fists clenched, possibly by now due to habit. She was discharged from the hospital on the sixtieth day, weighing 6 pounds, 11 ounces.

Laboratory studies showed a white blood count on admission of 14,500 cells per cubic millimeter with normal differential count. The hemoglobin was 11.5 Gm., the red blood count 3,030,000 cells per cubic millimeter. During the height of the diarrhea, the hemoglobin fell to 7 Gm., the red blood count to 2,650,000 cells per cubic millimeter, the white blood count was 12,900 cells per cubic milli-

meter. On discharge, the hemoglobin was 13 Gm., the red blood count 4,700,000 cells per cubic millimeter, and the white blood count 8,300 cells per cubic millimeter.

The patient returned a week later with a temperature of 105° F., severe clonic convulsions, and evidence of respiratory infection. Recovery was uneventful. The baby has been well ever since. At present (December, 1948) she weighs 10 pounds, 14 ounces. Physical examination showed her to be in perfect health.

#### COMMENT

There are many single reports of tetanus neonatorum in the literature, most of them with fatal outcome. There are only a few reports of larger series (Hines,<sup>1</sup> Jenkins,<sup>2</sup> Bratusch-Marrain,<sup>3</sup> and Jones<sup>4</sup>). The chief problem in this disease remains effective treatment. Perusal of the literature reveals that there really is only one drug which has lowered the mortality rate substantially, namely, magnesium sulfate. The use of this chemical in the treatment of tetanus of the newborn infant was first advocated by Bratusch-Marrain<sup>3</sup> in 1923. Between the years of 1906 and 1921, prior to its use, this author reports the loss of twenty-seven out of twenty-eight babies. From 1922 to 1923, he enlarged his series of patients by ten additional cases,<sup>5</sup> four of which survived. In the American literature, Hines<sup>1</sup> and Muehleli,<sup>6</sup> both in 1926, corroborated the effectiveness of the drug. In 1928, Smith<sup>7</sup> reported a case with recovery and was quite impressed by the effect of magnesium sulfate on the tetanic spasms. The actual value of antiserum, unless given very early after invasion of the organism, must still be considered doubtful. It should, of course, be administered in any case.

If called on to advocate a "standard" treatment, we would suggest the following routine:

1. Antiserum, 30,000 units, intramuscularly, to be repeated once or twice.
2. Adequate sedation with chloral hydrate, 5 or 6 gr., given every four to six hours as oil retention enema, with or without equal amounts of sodium bromide.
3. Magnesium sulfate, 50 per cent solution, 1 c.c. every six hours, given deep into the muscle.
4. Sodium phenobarbital, hypodermically, in addition to above, as needed to secure sedation.
5. Penicillin in oil every twenty-four hours.

#### SUMMARY

A case of tetanus neonatorum with recovery is reported. The use of magnesium sulfate is advocated. A "routine" treatment is suggested.

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# Clinical Conference

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## CLINICAL CONFERENCE OF THE DEPARTMENT OF PAEDIATRICS, VANCOUVER GENERAL HOSPITAL

### Case 1. A Case of Hemolytic Anemia in a Premature Infant

DR. PETER RANSFORD (Resident in Paediatrics) for DR. REGINALD WILSON (Associate in Paediatrics).—This white male infant was born two months premature on July 2, 1947. He was the first child and weighed 3 pounds, 4 ounces at birth. Mother, father, and child were Rh positive. The genotypes are detailed in Fig. 1. No atypical agglutinins were demonstrated. There is no history of jaundice or anemia on either side of the family. Except for a slight degree of physiologic icterus, the child was at no time jaundiced and did not bleed. However, he gradually became more pale until on Aug. 17, 1947, the hemoglobin was 54 per cent (7.04 Gm.). There was no splenic or hepatic enlargement noted at this time. He took his nourishment well and his diet was supplemented with multivitamin emulsion and iron. The stools and urines were normal. Two transfusions were given over a period of two weeks (August 18 to September 3) and after sixty-five days in the hospital he was discharged with a hemoglobin of 67 per cent.

He stayed at home for three weeks and during that time the pallor returned and on September 25 he was readmitted to the hospital with a hemoglobin of 55 per cent. Examination then revealed a pale infant weighing 7 pounds, 1 ounce. The abdomen was somewhat protuberant and the spleen was palpable. The remainder of the examination was negative. He was again transfused, which raised his hemoglobin to 60 per cent.

On September 30 refined liver extract was commenced and with this, plus oral iron, the hemoglobin hovered around 55 per cent but gradually fell during the next month to 45 per cent.

On October 27, the spleen was recorded as moderately enlarged with no other remarkable findings save pallor. He had continued to gain weight and now weighed 8 pounds. On November 3, in addition to liver and iron, folie acid was commenced with a subsequent rise in reticulocytes (see Fig. 1), and hemoglobin reached a maximum of 91 per cent by November 20 (an increase of from 50 per cent to 91 per cent in sixteen days). On December 2 the child was discharged on folie acid alone. The appetite was good and the color markedly improved. The spleen was still enlarged 3 fingerbreadths below the costal margin. Weight on discharge was 10 pounds.

Additional laboratory investigation revealed: red blood cell fragility normal on child and both parents, with no evidence of spherocytosis; volume index of .91; saturation index of .98; hematocrit 23 per cent. White blood count and differential were always within normal limits; icterus index on

November 5 was 18; Kahn, negative; sedimentation rate on October 28 was 5/16 (Westergren); stomach juice, histamine-fast achlorhydria; stools, normal in color; the urines were repeatedly negative for bile and showed urobilinogen values up to 1/64 dilution.

Bone marrow on November 1 gave a megaloblastic reaction (Figs. 2 and 3) and on November 18 was normal.

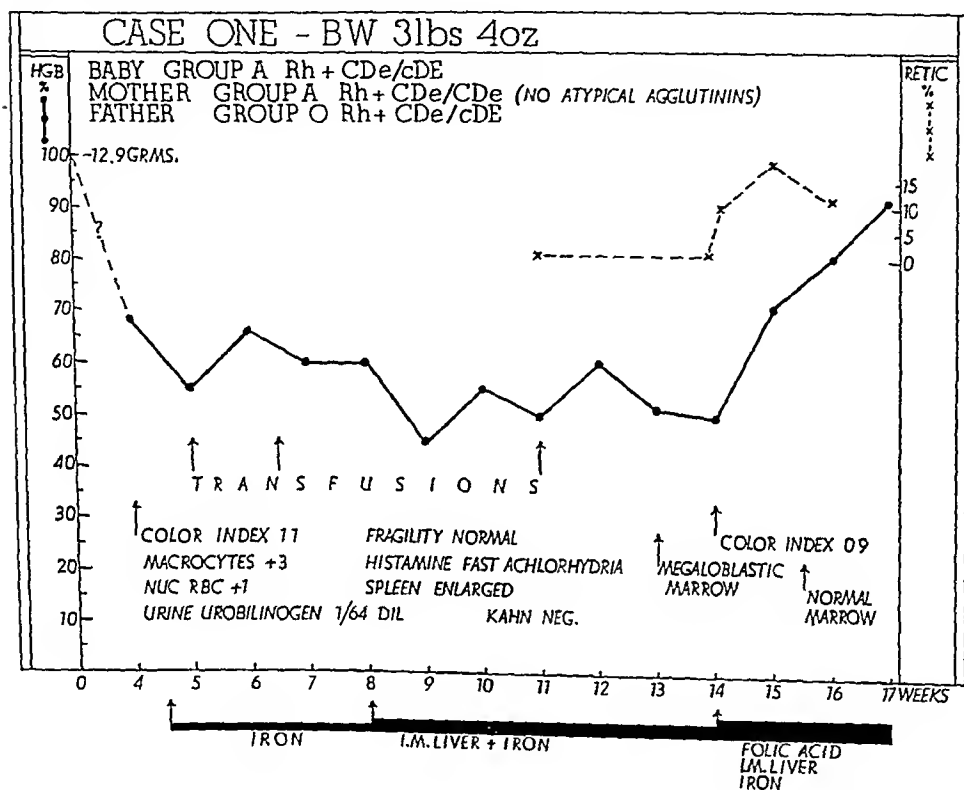


Fig. 1.—Diagrammatic representation of the main clinical features, treatment, and progress.

#### DISCUSSION

DR. A. W. BAGNALL (Associate, Department, of Medicine).—This is the case of a premature infant who developed a severe anemia. The onset of the anemia was earlier than the usual anemia of prematurity. It was a macrocytic and there was an increased urobilinogen excretion in the urine. It was a hemolytic type of anemia. There is no evidence that this was due to Rh incompatibility, yet one cannot say that some as yet unidentified agglutinin was not present. At any rate, the process was quite severe and prolonged as, in spite of transfusions, iron and refined liver extract, the infant remained anemic (hemoglobin 50) four months after birth.

There was a reticulocyte response from 2½ to 11 per cent after one day's treatment with folic acid. It seems unlikely that this was wholly due to this



treatment, but it would appear from the reversion of the bone marrow to normal after folie acid therapy and the quick and sustained rise in hemoglobin which occurred at this time, that there was a deficiency of that factor.



Fig. 2 —Low power magnification of the bone marrow smear.

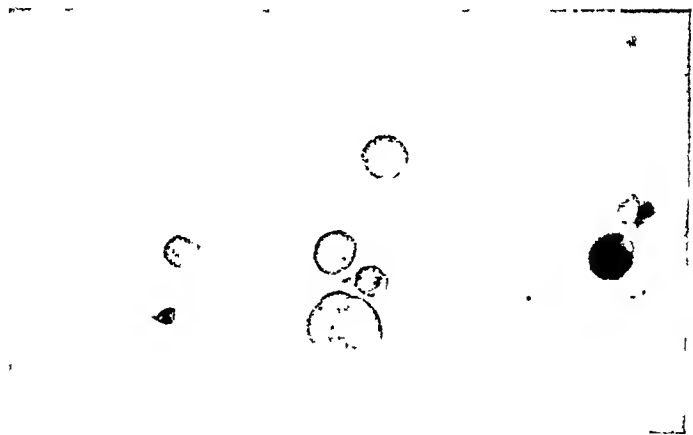


Fig. 3 —High power magnification showing typical "megaloblast"

In summary one must conclude that this child suffered a hemolytic (macrocytic) type of anemia due to some unidentified hemolysin. Certainly there is no positive evidence that this was due to excessive fragility or Rh compatibility. It would seem also that there was defective blood regeneration and that this was not improved by liver extract or iron but that regeneration *did* take place coincidentally with the administration of folie acid. We must conclude, therefore, that we are dealing with a hemolytic anemia in a premature infant with the secondary development of a folie acid deficiency.

DR. H. K. FIDLER (Pathologist).—It is difficult to establish a diagnosis in this case with absolute accuracy. I would like to comment upon the results of the bone marrow examination, which are particularly relevant. The term

"megaloblast" is used in the morphologic sense to designate that cell in the erythroid series corresponding to the abnormal cell found classically in the marrow of patients with pernicious anemia. Before folic acid therapy, the bone marrow revealed 5 per cent megaloblasts as well as macrocytocytes. Following treatment, all these cells had disappeared.

It is unfortunate that a better reticulocyte base was not established while the infant was on liver therapy. The failure to obtain an adequate response to parenteral liver may indicate a relationship to the so-called "archrestic" or "liver refractory anemia" of adults, in which folic acid therapy has shown a satisfactory response where liver has failed. The apparent lack of response to liver is in contrast to the majority of cases of infantile megaloblastic anemia reported in the literature.<sup>1</sup> We are justified in doubting the validity of specific reticulocyte response within twenty-four hours of commencement of therapy. However, the presence of megaloblasts in the marrow immediately before institution of folic acid therapy and after one month of liver therapy satisfies me that liver was ineffectual. I believe that this case is best classified with the group of macrocytic anemias of infancy, first reported by Zuelzer and Ogden<sup>1</sup> in 1946.

DR. REGINALD WILSON (Associate in Paediatrics).—We have presented this case as an atypical anemia in a premature infant. This infant had an anemia more severe and more rapid in development than is usual in the simple anemia of prematurity. The evidences of hemolysis, megaloblastic marrow, and splenomegaly also differentiate this case from the anemia usually seen in prematures. In the differential diagnosis one must also include:

1. Congenital hemolytic anemia (acholuric family jaundice). Fragility tests on the child and both parents excluded this.
2. Lederer's anemia. The age of onset and other clinical features such as fever and prostration described in Lederer's anemia were not present in this case.
3. Von Jaksch's anemia. This syndrome may well have included cases similar to ours. However, hemolytic anemias due to many other causes were also included in the classification described as "anaemia pseudo leucaemia infantum."
4. Syphilis and infection were excluded.
5. Megaloblastic anemia of infancy (Zuelzer).

This case has many features in common with the syndrome described by Zuelzer and Ogden, in that it developed a severe macrocytic anemia, the marrow was megaloblastic, folic acid gave a prompt reticulocyte response, and after this treatment the marrow returned to normal. However, the cases they described were in older infants, there was often an associated infection, and liver or folic acid produced a reticulocytosis.

In conclusion, I would like to point out, from our study of this patient, that hemolysis in the newborn premature infant will apparently exhaust the supply of certain essential hemopoietic factors and lead to a nutritional macrocytic anemia.

DR. DONALD PATERSON (Senior in Paediatrics).—Frankly, I was not previously aware of cases of this type. Zuelzer's work has emphasized that nutritional factors are involved in some of the macrocytic anemias of infancy. I have been interested in the presentation of this case, which illustrates a similar process.

Although I am assured that there was no evidence of Rh incompatibility in this infant, I am not satisfied that our knowledge of this factor is sufficient to say that it could not be operating here. Could this be a missed case of mild erythroblastosis? I would like to know if the genotypes have been checked and I would also like to know something regarding the child's present condition.

DR. REGINALD WILSON.—This child has been re-examined at the age of one year. He is normal hematologically, physically, and developmentally. There is no change in the Rh picture. The spleen is still enlarged.

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### Case 2. Chronic Pyuria (Congenital Defect) Presacral Sympathectomy (Final Report of a Previously Reported Case)

DR. E. LEHMAN (Assistant Resident in Pediatrics) for DR. A. F. HARDY-MENT.—Miss P. C., a white girl aged 15 11/12 years at the time of her death in November, 1948, was the subject of a report in the JOURNAL<sup>1</sup> when she was 14 months of age. At that time she had had a left presacral sympathectomy done in an attempt to relieve a demonstrated left hydroureter with reflux from the bladder on that side. There was x-ray evidence of some degree of hydronephrosis on both sides preoperatively with some reflux from the bladder to the right ureter also (Fig. 4). However, postoperatively it was felt that "there was decrease in size of the bladder and ureter."

The child was presented at that time as "a case of persistent pyuria due to a neuromuscular dysfunction of the bladder for which a presacral sympathectomy was done." No obstructive lesion was found anywhere in the urinary tract.

On discharge from the hospital, two months after the operation, the urine contained *Bacillus coli*, a faint trace of albumin, and 1 to 2 white blood cells per high power field.

It would appear justified to report the progress of this girl during her remaining years and the remarkable findings at autopsy.

Approximately seven months postoperatively her urine showed 4 plus white blood cells with clumping, a very occasional granular cast cell and red blood cells. *B. coli* were cultured from the urine.

In 1935, grand mal type seizures began, continued during the next five years, and ceased without explanation during early 1940. During this time she had many attacks of "pyelitis." In March, 1940, several examined specimens were clear.

In November, 1943, she was reported as having no convulsions, was sociable but irritable, and was not doing well at school. At this time she had pyuria which was controlled by sulfonamide and mandelic acid.

In December, 1946, the urine showed albumin from a trace to 2 plus, and a few pus cells. She was "slightly anemic."

In March, 1947, the pyuria was reported as not responding to the sulfonamide and mandelic acid. *B. coli* were cultured from the urine.

In November, 1947, a year before her death, she was investigated in the hospital. A Mosenthal test showed specific gravity from 1.009 to 1.011; hemoglobin, 70 per cent (9.11 Gm.); leucocyte count, 3,800; nonprotein nitrogen 50. Catheterization of each ureter showed 4 plus pus on right side and 2 plus on left side. No organisms were grown.

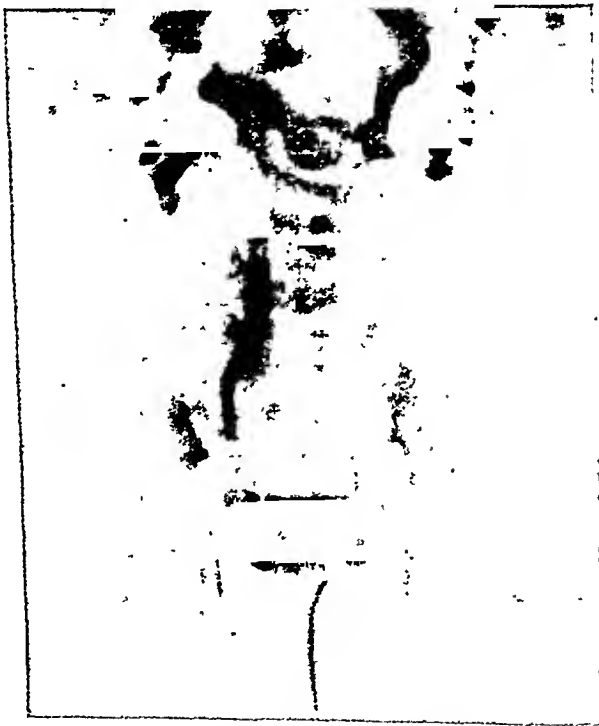


Fig. 4.—Pyelogram, Jan. 16, 1934.

At each visit above noted, blood pressure readings were attempted but the results were never considered to be accurate because of the attitude of the patient.

In July, 1948, there is a report that "the patient has grown into quite a tall, young girl, rather nice looking, but is immature emotionally and requires patient and consistent encouragement at school; otherwise her progress is satisfactory, is very introspective and has a feeling of insecurity as to her own ability."

In September, 1948, when first seen by us, she was reported to have recently developed a violent temper and no interest in her personal appearance. She

complained of occasional headaches relieved by Aspirin. For two weeks she had had frequent nausea and vomiting. On Sept. 28, 1948, urine showed albumin 3 plus and an occasional white blood cell. Hemoglobin 52 per cent (6.76 Gm.), red blood cells 3,000,000, white blood cells 5,400, sedimentation rate 82 mm. in one hour; nonprotein nitrogen 103, blood pressure 148/70, pulse 98, temperature 99.1° F. Scattered rhonchi were heard in the chest. Chest x-ray was negative. She was admitted to the hospital September 30.

A Mosenthal test showed fixed specific gravity of 1.010. The fundi showed mild edema with a fresh, small hemorrhage on the right side.

She was noted to have a positive Chvostek's sign, uremic breath, an enlarged heart, and sacral edema.

On Oct. 24, 1948, massive subconjunctival hemorrhages developed. Copious vomiting was present. All treatment was of no avail; i.e., no diuresis was produced.

On Nov. 1, 1948, violent convulsions occurred. Terminally the patient was deeply unconscious with edema of the extremities. On November 6, nonprotein nitrogen was 167. She expired on Nov. 11, 1948. Plasma chlorides were 540 mg per 100 c.c. on October 20 and 492 mg. per 100 c.c. on October 30.



Fig. 5—Gross appearance of kidneys and ureters. Note large circumscribed nodule of fibrous tissue in left kidney.

DR. H. K. FIDLER (Pathologist).—The post-mortem examination was carried out twenty-three hours after death. The right kidney weighed 60 grams and the left 30 grams (normal 100 to 150 grams). Each kidney was small, markedly distorted, nodular, and firm in consistency. The capsule stripped with difficulty, causing some decortication. The cut surfaces showed moderate dilatation of

pelvis and calyces. The cortex was reduced to a narrow zone about one-half normal thickness and much of the corticomedullary differentiation was lost. In each kidney there were several circumscribed nodules of pale, yellowish-brown, homogeneous tissue of soft, fibrous consistency, measuring up to 2 cm. in diameter (Fig. 5). The ureters were dilated to about twice normal size and their walls were quite thickened (Fig. 5). The ureteric orifices in the bladder showed normal patency and the bladder appeared essentially normal.

The heart was enlarged, weighing 300 grams, and the left ventricle measured a maximum of 13 mm. in thickness. A small amount of atherosclerosis was noted in the aorta.

Each lung weighed approximately 540 grams (normal 300 to 400 grams) and showed patchy, pneumonic consolidation of the lower lobes.

Microscopic examination confirmed the impression of chronic pyelonephritis. There was marked destruction of glomeruli and tubules with replacement by fibrous connective tissue and a chronic inflammatory infiltrate.

The circumscribed nodules seen macroscopically proved to be loose, fibrous, connective tissue containing only scattered atrophic tubules. The ureter showed marked submucosal fibrosis but the muscle layers appeared essentially normal. Sections of the lung confirmed the diagnosis of bronchopneumonia.

No conclusion can be reached concerning the primary etiology of the renal lesion other than the fact that it was not on the basis of any organic obstructive lesion of the urinary tract. It would be consistent with a neuromuscular dysfunction in which chronic bacterial infection resulted in marked destruction of renal tissue causing renal decompensation and hypertension.

DR. H. L. CHAMBERS (Assistant in Urology).—This case presents the typical clinical and pathologic picture usually found in the condition commonly called "megalo-ureter" or "congenital idiopathic dilatation of the ureter." That is, it shows marked dilatation of the ureter with gaping orifices and without any demonstrable mechanical obstruction.

The etiology is still not settled. It may be due to some disturbance in the neuromuscular control of the ureter and bladder. Other possible causes that have been suggested are hypoplasia of the musculature and absence of the normal inhibition of ureteral growth at the fifth month of fetal life.

The treatment of megaloureter is difficult. A left presacral sympathectomy was done in this case, no doubt on the theory that the sympathetic supplies inhibitory fibers to the detrusor and motor fibers to the internal sphincter and smooth muscle of the proximal urethra. This might contribute to the dilatation of the bladder and ureter. However, the actual role that the sympathetic and parasympathetic systems play in ureteral function is not definitely established. Lapiès,<sup>2</sup> in a recent report on the physiology of the human ureter, found that ureteral peristalsis and tone were not affected by blockade or by stimulation of the sympathetic and parasympathetic nervous systems. Thus he concluded that the ureter is an autonomous organ. If this be so, it is difficult to understand how sympathectomy has anything to offer these cases. At any rate, it is apparent that the procedure was of very little, if any value in the case under discussion.

DR. DONALD PATERSON (Senior in Paediatrics).—I think that this case was typical of the end result in long-continued pyelonephritis which was obviously bilateral. Over the years these cases have demonstrated that quite considerable periods are common when the urine might be clear and no fever present, then bouts of fever with pus occur, almost certainly due to miliary renal abscesses draining into the pelvis of the kidney. The final result, namely, bilateral renal fibrosis with uremia and high blood pressure, is typical of such a renal lesion. The lesson to be learned is for the condition to be diagnosed and strenuously treated with modern antibiotics. A month's or two months' treatment might be necessary at the onset. Where the infection is confined to one kidney due to a malformation, nephrectomy would result in a cure. A sedimentation rate is an extremely valuable aid in ascertaining the cessation of such a renal infection.

DR. A. F. HARDYMENT (Assistant in Paediatrics).—Through the years that passed between the operation on this child and her death, many efforts were made to control her infection. Sulfonamides and antibiotics were not available during the earlier years. Later on there was little, if any, cooperation with the attending pediatrician. At any rate, infection finally completely destroyed her kidneys.

If we see such a case today with bilateral megaloureter, we can only attempt to control the infection. If the condition is unilateral we must remove the infected kidney. The present case illustrates the fact that presacral sympathectomy is not of value in relieving the condition.

This is a final report on a previously reported case.

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### Case 3. A Case of Polyostotic Fibrous Dysplasia (Albright's Syndrome)

DR. A. MALKIN (INTERN), FOR DR. JOHN PITERS.—This patient (M.G.) is a white female child  $5\frac{1}{2}$  years old who was admitted to the Vancouver General Hospital on May 30, 1948, with the complaint of vaginal bleeding. She had been well up to May 20, ten days prior to admission, when she developed crampy abdominal pain which persisted on and off for the entire day. The following morning she began to have vaginal bleeding which continued for about one week, requiring the use of several napkins daily and being fairly typical of a normal menstrual period. The flow had ceased by the time of admission. The mother was also concerned by the patient's increasing obesity. She had always been a large and sturdy child, enjoying good health and showing better than average intelligence, but for the past eighteen months she had seemed hungry all the time and had become markedly obese. She was troubled frequently by enuresis. It was elicited that a wood tick had been removed from the back of her head on May 17 and another found partly embedded and removed on May 23.

The patient's birth history and early development were normal. The past history was negative except for frequent attacks of tonsillitis. The family history was essentially negative. There are three male siblings, all apparently normal in stature and appearance. There was no evidence of familial endocrine abnormality.



Figs 6 and 7.—Front and side view of the patient.

Physical examination (Figs. 6 and 7) revealed a large and obese child, 48 inches tall and weighing 81 pounds. The breasts were enlarged with definite pigmentation of the areolae. This breast enlargement was partly due to increased fat deposition and partly to hypertrophy of the glandular tissue, which felt firm and seemed about 3 cm. in diameter. There was no pubic or axillary hair. The skin was normal in appearance except for a triangular, sail-shaped area of pigmentation in the left suprascapular area, extending laterally from the midline. This area measured 8 cm. in the vertical diameter and about 6 cm.





Fig. 8.—X-ray showing dysplasia in humerus and radius.



Fig. 9.—X-ray of hands showing dysplasia of bones.

at the base. The pigmented skin was not elevated. The scalp, eyes, ears, and nose were essentially clear. The tonsils were markedly enlarged and cryptic. Three of the 6-year molars and the two lower permanent incisors were present. The heart and lungs were negative. The blood pressure was 104 systolic and 74 diastolic. The spleen was barely palpable. The genitalia showed slight but definite enlargement. The nervous system showed no abnormalities.

The laboratory investigation was as follows: urine analysis, negative; red blood cell count, 4.2 million; hemoglobin 76 per cent; blood calcium, 10.7 mg. per cent; blood phosphorus, 6.4 mg. per cent; alkaline phosphatase 19.7 Bodansky units; nonprotein nitrogen 24 mg. per cent; cholesterol, 143 mg. per cent; fasting blood sugar, 99 mg. per cent; glucose tolerance test following 70 Gm. of glucose orally showed a rather flat curve; the 17-ketosteroid excretion was recorded as 0.744 mg. of androsterone per day; stained vaginal smears showed a typical postmenstrual appearance.

The x-ray examination of the skull, spine, and ribs was negative. The pituitary fossa was within normal limits. Some definite change was noted in the upper end of the shaft of the left radius (see Fig. 8), where the normal architecture has been replaced by an amorphous appearance. There is a suggestion of an amorphous type of change in the left ulna and in the medial half of the lower end of the left humerus as well. The left hand (see Fig. 9) shows marked broadening of the shafts of the metacarpals throughout, with great thinning of the cortex and irregularity of architecture consisting of absorption of some and increase of other striae. The middle phalanges of the index and ring fingers show very marked broadening of the shaft with a uniform amorphous appearance of the bone. The proximal phalanx of the ring finger shows a somewhat less pronounced but somewhat similar appearance, with a combination of rarefaction as well. The distal phalanx of the ring finger is grossly broadened with quite a wide tuft so that its volume is probably twice that of the corresponding phalanx of the other hand. The right hand is relatively normal but the first metacarpal shows a broadening of the shaft with some irregularity of the architecture. The proximal phalanx of the thumb shows a somewhat similar change. The development of the hands resembles that of a child nearer 12 years of age than 6. The right humerus shows a very slight thinning of the cortex in the middle third of the shaft. The femora, tibiae and fibulae show only a number of horizontal nutritional lines.

DR. JOHN PETERS (Attending Pediatrician).—This patient is an example of a clinical syndrome first described by Albright in 1937. While still referred to as the Albright syndrome, the newer name of *polyostotic fibrous dysplasia* is more descriptive and seems to have been generally accepted. In this condition bone lesions showing *osteitis fibrosa* are associated with areas of pigmentation of the skin and a generalized endocrine dysfunction. When the disease occurs in female children precocious puberty is an added feature. The bone lesions may be single or multiple, are usually predominantly unilateral, and frequently are segmental in distribution. The characteristic pigmentation is patchy, tending to appear on the same side and having the same segmental

distribution as the bone lesions. The endocrine dysfunction may produce effects such as premature osseous development and maturation, hyperthyroidism, or precocious sexual development. The skeletal lesions constitute the central feature of the disease and usually progress slowly to cyst formation with a tendency to spontaneous fracture.

In this case the bone lesions are early and could have been easily missed if one had not deliberately looked for them. The important clue which directed our attention to the skeletal system was the area of pigmentation in the left suprascapular region. The medial border of this area ended so evenly at the midline over a distance of some 8 cm., that it suggested the pattern of cutaneous nerve distribution. It is interesting to note that the most marked bone changes, (in the left radius, metacarpals, and phalanges) and the skin pigmentation occur in regions supplied by approximately the same lower cervical nerve roots. If these bone changes had not been discovered, several other diagnoses would have to be ruled out. The presenting feature of precocious puberty could have resulted from a granulosa cell tumor or cyst of the ovary. Here one might have palpated an enlarged ovary or discovered an unusually high level of excretion of urinary estrogen. In polyostitic fibrous dysplasia, estrogen excretion varies with the menstrual cycle and is within physiologic limits. One also would have considered a lesion in the region of the midbrain, with pituitary irritation and stimulation. However, this patient has no evidence of an intracranial lesion. Oddly enough, there is no record of sexual precocity ever arising as a result of an actual tumor of the pituitary gland itself, although such a change has been noted following either neoplastic or inflammatory involvement of the midbrain. Hyperparathyroidism frequently has been confused with the Albright syndrome because of the somewhat similar bone lesions. The normal serum calcium and phosphorus determinations rule out hyperparathyroidism in this case. Hyperplasia or tumor of the adrenal cortex may produce early sexual development, but such changes tend to be heterosexual, with marked enlargement of the clitoris, early development of pubic and axillary hair, and other evidence of virilism. Our patient shows no masculinizing changes at all. She does show obesity of a marked degree. This is probably on the basis of pituitary dysfunction, although it has been suggested that the pituitary acts through stimulation of the adrenal cortex with overproduction of a so-called S-hormone.

Dr. Harrison, would you like to discuss the x-rays in this case?

DR. BEDE HARRISON (Chief of Department of Radiology).—The osseous lesions are visible bilaterally but they are more prominent on the left side. They are of three types: (1) There appears to have been complete absorption of lime, leading to a cystic appearance, the cysts being irregular in outline and spread along the long axis of the bones. These are well exemplified in the case of the left humerus. (2) An amorphous appearance as though the lime, instead of being limited to the architectural striae, is diffusely scattered through the whole of the tissue, exemplified particularly in the case of the left radius. (3) Destruction of the horizontal striae with retention and increased visibility of the longitudinal striae, well exemplified in the upper end of the left ulna.

DR. J. PETERS.—Would you tell us how the bone lesions in this case can be differentiated radiologically from hyperparathyroidism?

DR. B. HARRISON.—In hyperparathyroidism the lesions are generalized. Here they are spotty in distribution. The distribution of these lesions as well as their varied character is indicative of a polyostotic fibrous dysplasia.

DR. J. DAVIES (Chief of Department of Pediatrics).—Dr. Fidler, can you tell us something about the pathology of this condition?

DR. H. K. FIDLER (Chief of Department of Pathology).—This case would appear to fulfill the diagnostic criteria for the syndrome first described as "osteitis fibrosa disseminata" by Albright<sup>1</sup> and later termed "polyostotic fibrous dysplasia of bone" by Lichtenstein.<sup>2</sup> The lesions in bone consist of solid fibroblastic hyperplasia which fills the marrow cavity, causing resorption of bone and thinning of the cortex, although no new periosteal bone is deposited. The lesion may be distinguished from osteitis fibrosa cystica by the frequent presence of small islands of cartilage and the absence of cyst formation, although radiologically the bone lesion may appear cystic. It is often difficult, however, to distinguish between these two lesions on histologic grounds alone. The clinical, biochemical, and x-ray findings in this case appear adequate to establish the diagnosis without resort to biopsy.

The etiology is unknown but it has been thought to be a manifestation of some underlying trophic disturbance, possibly related to pituitary dysfunction, or it may be the result of an embryologic defect of bone. Recently it has been suggested that the monostotic and polyostotic types of fibrous dysplasia are unrelated etiologically<sup>3</sup> although such an hypothesis begs the question when the cause of neither is established.

DR. WILLIAMS (Intern).—I would like to ask Dr. Eden how he interprets the estimations for serum phosphatase and 17-ketosteroids.

DR. J. EDEN (Chemical Pathologist).—The excretion of 0.744 mg., as androsterone in twenty-four hours is within normal limits for this age group and assuming that all urine voided during the collection period was saved, it indicates that the adrenal cortices are not oversecreting the hormones of which 17-ketosteroids are a degradation product.

The serum alkaline phosphatase level of 19 Bodansky units is pathologic in a child of this age, but high levels have been repeatedly reported in this disease and appear to be an integral part of the syndrome. The enzyme is elaborated by the osteoblasts and is concerned with the impregnation of the bone matrix with calcium salts.<sup>4, 5</sup> A high serum alkaline phosphatase level, therefore, can be interpreted as evidence of an attempt to repair or limit the lesions by increasing surrounding calcification. However, in this case the x-rays do not suggest any increase in the density of the bone surrounding the lesions.

More recently it has been suggested that the enzyme is mainly concerned with the formation of the fibrocollagenous framework of bone,<sup>6</sup> and so it is also possible that the elevated serum levels are the direct result of the overproduction of the fibrous matrix which occurs in this disease.

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## Case 4. Cortical Carcinoma of the Adrenal Gland

DR. ELSA LEHMANN (Assistant Resident in Pediatrics).—This patient, G. W., a 17-month-old white boy, became feverish and listless two days before admittance to the Vancouver General Hospital on Sept. 28, 1948. During this time he could take only fluids, most of which he vomited. Because of these symptoms his family physician was called, who discovered a mass in the left upper quadrant and advised hospitalization.

Prior to this illness he had always been well and his parents had not noticed any change in his appetite or energy, nor did they consider that he had become paler.

Physical examination revealed a fairly well-developed and well-nourished child. His face was flushed and his eyes somewhat sunken. He whined continuously and appeared miserable. Temperature was 104° F., pulse 130, respirations 25, weight 11.3 Kg.

A mucopurulent nasal discharge was present. The pharynx was moderately inflamed. The ears, superficial glands, skin, respiratory, cardiovascular, nervous, and osseous system presented no changes.

The abdomen was flaccid and no tenderness was present. The liver and spleen were not enlarged to palpation. There was a large, firm mass about the size of a small grapefruit in the left upper quadrant extending from the costal margin to the level of the umbilicus, and from the flank to the midline; it was not tender and was only slightly movable. The external genitalia were of normal size and configuration and no pubic hair was present.

*Laboratory Investigation.*—The urine contained 1 plus albumin and 2 plus white cells in clumps. Red blood cells were 4.1 million; hemoglobin 11 Gm.; white blood cells 24,000 with a fairly marked shift to the left; platelets 269,000; nonprotein nitrogen 28 mg. per cent.

The patient was given 10,000 units of penicillin every three hours upon admittance, and two days later 5 grains of sulfadiazine every six hours in an attempt to clear up the urinary tract infection. After the first two days the temperature ranged between 99° and 100.6° F. Subsequent urinalyses were repeatedly negative.

An intravenous pyelogram was done on October 1, showing a large soft-tissue swelling in the left upper quadrant. Following the injection of the dye the right kidney appeared normal; the left, however, was displaced downward. The superior calices appeared normal in so far as visualized. Filling was not so complete as on the right, possibly due to pressure. The lack of gross de-

formity of the calices on the left suggested that the tumor was extrinsic, although the possibility of a tumor in the periphery of the kidney could not be excluded altogether.

On October 4 the patient was given a transfusion of 150 c.c. of whole citrated blood and the following day, under ether anesthesia, a well-encapsulated tumor of the left adrenal gland was removed through a left kidney incision without difficulty by Dr. George Langley. No metastases were visible at operation.

Postoperatively the patient received 250 c.c. of whole blood and 500 c.c. of normal saline intravenously. The immediate postoperative course was uneventful.

The pathologic specimen consisted of an encapsulated, fleshy mass measuring 9 by 9 by 4 cm. The outer surface was smooth and glistening, although somewhat lobular in appearance. The cut surface was composed of reddish-brown, soft, friable tissue.

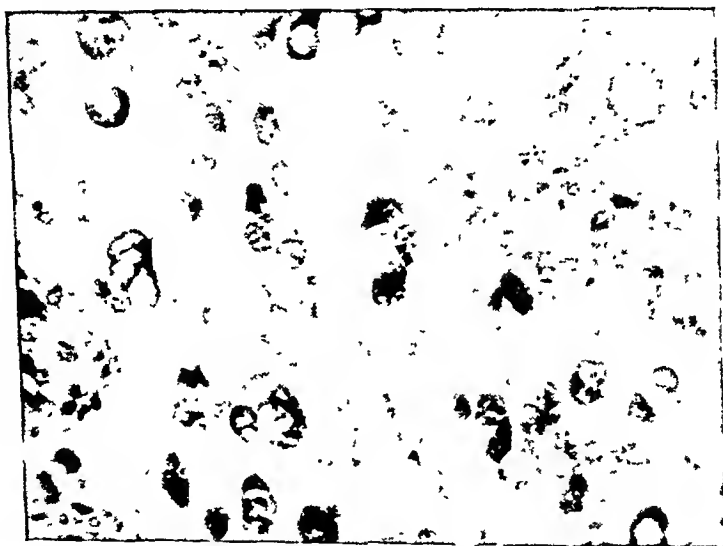


Fig. 10.—Section showing giant cells.

Histologic sections taken through the tumor mass revealed a sparse fibrotic stroma, supporting sheets of hyperchromic pleomorphic and polymorphic epithelial cells showing marked variation in size and shape, with numerous giant forms (Fig. 10). The nuclei were large and vesicular and contained numerous mitotic figures. The cytoplasm was sparse and in the larger cells was of an eosinophilic, granular nature. The stroma was heavily infiltrated with lymphocytes. The conclusion was giant cell carcinoma of the adrenal cortex.

*Subsequent Course.*—On October 18 deep radiation therapy was instituted, ten treatments being given between this date and on October 31. He was discharged on October 31 weighing 10.6 Kg.

*Laboratory Data.*—Red blood cells were 4.0 million; hemoglobin 9 Gm. per cent; white blood cells 5,000.

He was readmitted on Dec. 5, 1948, because of increasing pallor, lassitude, and abdominal distention. There was a general deterioration in his condition since he was last seen. He appeared paler and more irritable and presented a picture compatible with advanced malignant disease. The most significant change was the marked enlargement of his abdomen, which was due to a marked increase in the size of the liver. This organ extended into the right iliac fossa and was very firm and nodular in consistency. A moderate amount of ascitic fluid was present.

*Laboratory Data.*—Red blood cells 3.2 million; hemoglobin 6 Gm. per cent; white blood cells 15,000, of which 80 per cent were granulocytes.

The patient was removed by his parents after five days in the hospital, and died at home Dec. 29, 1948. No post mortem was granted.

DR. E. STEWART JAMES (Attending Pediatrician).—When this patient was first seen we thought the most obvious diagnosis was Wilms' tumor because of the size and location of the mass. After seeing the pyelograms which showed an almost normal kidney pelvis displaced downward, we thought the mass more likely to be extrinsic, probably adrenal, in origin. A Wilms' tumor, however, could not definitely be ruled out on this evidence. If the tumor were adrenal in origin it was thought that it was probably a neuroblastoma, because no signs of cortical dysfunction, such as virilism or Cushing's syndrome, etc., were present. Actually, an adrenal cortical tumor was not suspected, and for this reason the output of 17-ketosteroids in the urine was not measured. After we had received the pathologist's report we were a little uncertain as to what the prognosis would be, although we presumed it was very poor. Dr. Langley, as Dr. Lehmann has pointed out, was able to remove the tumor without great difficulty, and he saw no metastases. Following operation the patient received what was considered adequate radiation therapy. In spite of this the patient's course was rapidly downhill in the next two months, with marked metastatic enlargement of the liver.

DR. H. K. FIDLER (Pathologist).—The tumor in this child showed the histologic appearances of a malignant neoplasm. Two types of cell are seen, giant cells on the one hand, with abundant eosinophilic cytoplasm and extremely hyperchromatic nuclei, and elsewhere solid masses and irregular cords of small cells with relatively little cytoplasm but showing irregular and coarse nuclear chromatin structure. It is this small cell which is probably the more malignant in this tumor because several thin-walled blood vessels were found containing clumps of these cells (Fig. 11). Metastatic tumors would be expected ultimately in the lungs and possibly liver.

It is of interest to note the clinical lack of any hormonal activity. Such an association is common in the highly malignant tumors of the adrenal cortex but by no means invariable. In fact, the hormonal activity of the tumor cannot be determined with any degree of certainty by the degree of differentiation found.

DR. BEDE J. HARRISON (Radiologist).—Giant cell tumors of the adrenal glands have been reported variously as being responsive and unresponsive to x-radiation, but in view of the fact that the adrenal cortex arises from the same anlage as the testis, I feel that these tumors should be given the opportunity that radiation affords. This patient, therefore, was treated along the lines laid down for treatment of the seminomas in that not only was the local tumor area irradiated but the glandular areas extending from the tumor as far upward as the neck were also included in the fields of treatment. However, the patient's blood picture rapidly deteriorated and treatment was ceased when he had received 1,000 r. When the question of further treatment came up he was discovered to have a large mass in the right upper quadrant, so no further treatment was given.

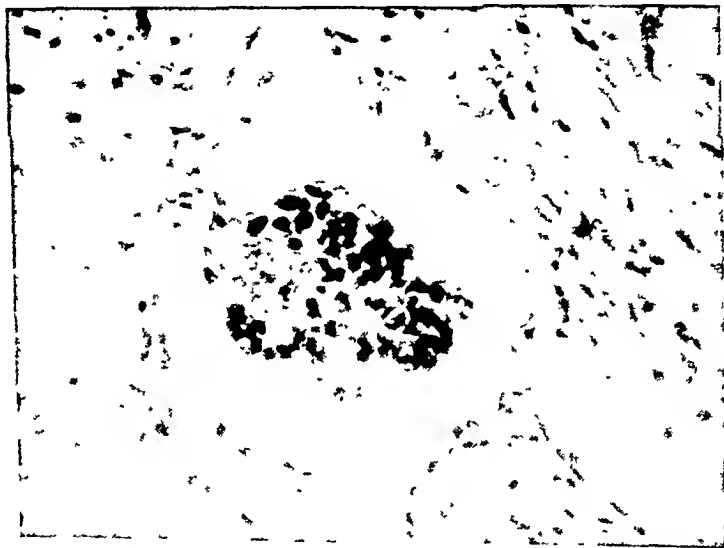


FIG. 11.—Clump of small type malignant cells in blood vessel.

DR. E. STEWART JAMES.—One assumes that this type of tumor must be quite rare, judging by most modern pediatric texts, in which little or no space is devoted to the subject, attention being focussed on those cortical carcinomas which are associated with sexual precocity, etc. The rapid deterioration of this patient to a fatal termination illustrates the point made by Dr. Fidler that cortical carcinomas in which hormonal activity is not in evidence clinically are usually highly malignant.



# Psychologic Aspects of Pediatrics

## THE HOME CARE OF THE PREMATURE INFANT

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NEWCASTLE-ON-TYNE is an industrial community in northeastern England with a population of about 280,000. Housing conditions in this busy mining town have been poor for a number of years; since the war they have deteriorated further. As in the rest of England, and the Continent as well, a large proportion of the babies are delivered in the home by trained midwives. Each year approximately 300 living premature infants (infants weighing  $5\frac{1}{2}$  pounds or less) are born in Newcastle-on-Tyne, somewhat less than one-half of these in the home.

In 1945 a program for the home care of premature infants was initiated. A corps of nurses was specially trained for this purpose and an ambulance service organized to deliver special beds, blankets, and other equipment, to the home if necessary. The maximum number of infants taken care of by one nurse is three; more usually she attends to two. Any medical practitioner may call for assistance by telephoning the maternity hospital.

Owing to the shortage of nurses, it was not possible for all premature infants born at home to have this specialized care and it has, therefore, been possible to compare not only the results of home and hospital care, but also the value of specialized over routine care in the home.

A preliminary report of the results for the first seventeen months appeared in 1947.<sup>1</sup> Recently the results of a three-year study have been reported.<sup>2</sup> During the entire three-year period 379 premature infants were born at home and 537 in hospitals. The over-all case fatality rate for those born and cared for in the home during the first twenty-eight days of life was 27.2 per cent and for the hospital group 19.5 per cent, a decided difference in favor of the hospital group. When, however, the home group receiving special care (159 infants) was compared with the hospital group, no difference in case fatality was found.

A comparison of the fatality rates by weight at birth of the babies born and specially cared for in the home in Newcastle-on-Tyne and those supervised in American hospital units<sup>3</sup> is shown in the chart. The American figures were compiled during the years 1940-1945 and are representative of the best results obtained in special premature stations. Unfortunately the British results have been expressed in pounds, the American in grams. Moreover, the British series is relatively small.

The results with the specialized care in the home strongly suggest that infants weighing  $3\frac{1}{2}$  pounds and over can, as a rule, be taken care of at home fully as well as in a special hospital premature unit.

Certain uncontrollable selective factors were operative in Miller's study, as is so frequently the case in studies with human material. For example, special aid was often sought for the small infants when there seemed to be a

chance for their survival, a factor which would favor the results in the group receiving special care. On the other hand, a factor operating against Miller's results was the fact that special nurses were often summoned when a larger infant was thought to require special attention.

Miller raises the question whether it is wise to attempt to provide hospital accommodation for all premature infants. It is his opinion that indiscriminate hospitalization for babies weighing over  $3\frac{1}{2}$  pounds is not warranted. Home care is not only safer from the point of view of infection and more economical; it has, in addition, he believes, a wholesome effect in promoting family ties and solidarity. This was not anticipated when the service was started but its significance and importance soon became apparent. Miller states: "The nurse in her role of teacher and adviser and by her personality mobilizes the family for duties: someone to watch at night; someone to watch during the day; someone, probably a neighbor, to shop; everyone interested is involved and all have a sense of achievement, which gives the child a good start and is far better than if he were taken away to a hospital and returned a month or six weeks later, an unknown infant, feared and strange."

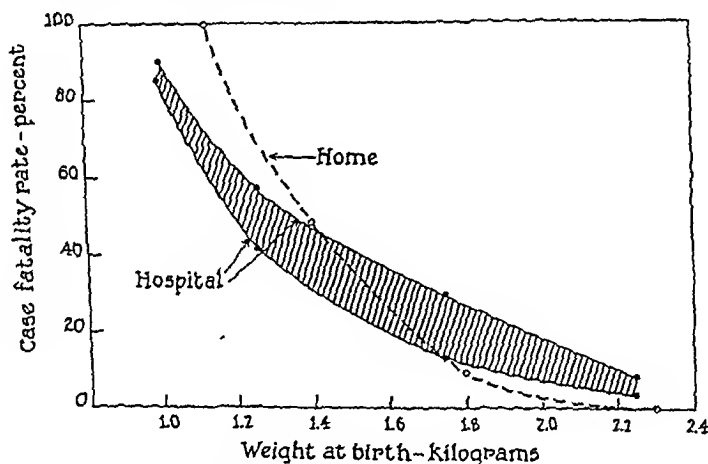


Chart 1.—Comparison of the case fatality of premature infants, specially cared for in the home and in hospital premature units.

The technique of caring for premature infants in the home with the help of specially trained nurses is one which requires careful consideration. If the larger infants who constitute a majority of the occupants of a premature unit can be taken care of at home, premature units will be relieved of a tremendous burden and more time will be available for the care of the smaller members. Moreover, a source of infection will be removed. In addition to the advantages enumerated by Miller, the psychologic trauma of separating parents and newborn infants will be eliminated and parental overanxiety lessened.

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# Comments on Current Literature

## ADVANCES IN ANTIBIOTIC THERAPY

CONSIDERING the phenomenal advance of knowledge concerning antibiotics within the past few years, it is not surprising to hear of major contributions in this field. However, two very significant contributions are reported in current literature which deserve special comment. In the March 25, 1949, issue of *Science*, Selman A. Waksman and Hubert A. Leechevalier<sup>1</sup> announced the isolation of neomycin, a new antibiotic active against streptomycin-resistant bacteria, including the tuberculosis organisms. Since 1939 Waksman and his associates have tested for activity against various bacteria many thousands of cultures, largely actinomycetes belonging to the genus *Actinomyces* (*Streptomyces*) which were isolated from soils, composts, peats, and other natural substrates.

Five years ago the isolation of streptomycin from *Actinomyces* (*Streptomyces*) *griseus* was announced. Since then streptomycin has proved itself invaluable in the treatment of a number of disease entities, and it has been especially important in the therapy of tuberculosis. However, certain serious limitations of streptomycin are well known, particularly its neurotoxic potentialities, and, on its prolonged administration, the tendency for the development of resistance among the infectious organisms. Favorable results obtained with dihydrostreptomycin, a reduced form of streptomycin, seem to indicate that the toxic reactions can be overcome, in part at least. The development of resistance among infectious organisms on prolonged administration of streptomycin constitutes a serious limitation, especially in the treatment of tuberculosis.

The isolation of neomycin from *Actinomyces fradii* (*Streptomyces fradii*) is a major contribution to our knowledge since this antibiotic is effective not only in its action against many gram-positive and gram-negative bacteria, especially mycobacteria, but has been shown to be effective likewise in the treatment of known streptomycin-resistant strains. To date the toxicity of this new agent seems to be considerably less than that of streptomycin. The authors list several desirable properties of neomycin: "(1) similar activity against both streptomycin-sensitive and streptomycin-resistant bacteria; (2) considerable activity (in some cases greater activity than streptomycin) against various forms of *M. tuberculosis* and other mycobacteria; (3) limited toxicity to animals or none; (4) activity against various bacteria *in vivo*, including Gram-positive and Gram-negative organisms and against both streptomycin-sensitive and streptomycin-resistant organisms; (5) lack of resistance against neomycin among the organisms sensitive to it, or only limited development of such resistance."

With the isolation of neomycin a new opportunity for important advances in the treatment of human tuberculosis is presented, and clinicians will watch with interest for reports of the use of this newly isolated antibiotic.

Another significant advance in antibiotic therapy is described in a report by Joseph E. Smadel, Elizabeth Jackson, Herbert Ley, Jr., and Raymond Lewthwaite,<sup>2</sup> which appears in the February (1949) issue of the *Proceedings of the Society for Experimental Biology and Medicine*. This group of investigators present data resulting from careful comparative studies of the effectiveness in

rickettsial and viral infections of chloromycetin (chloramphenicol) from two sources: from fermentation liquor of cultures of *Streptomyces venezuelae*, N. Sp., and obtained by chemical synthesis.

The announcement by Crooks and his co-workers<sup>3</sup> that chloromycetin may be prepared synthetically is important news. Smadel and his group have shown experimentally that the effects of synthetic chloromycetin and fermentation chloromycetin are essentially identical on the rickettsiae of epidemic typhus, murine and scrub typhus, on those of spotted fever and rickettsial pox, and on the viruses of psittacosis and lymphogranuloma venereum. Chemotherapeutic studies of the two types of chloromycetin were carried out in embryonated hen's eggs and in mice. In each instance similar results were obtained with the two forms of the antibiotic.

A preliminary account of the effect of synthetic chloromycetin on patients with typical scrub typhus is presented. The response of these two patients following therapy was comparable to that observed in other cases of scrub typhus which had been treated with fermentation chloromycetin. The same low level of toxicity reported for fermentation chloromycetin holds true apparently for synthetic chloromycetin. In addition to the purely scientific importance of such a synthesis, it seems reasonable that synthetic chloromycetin will make available to clinicians a far greater supply of this remarkable antibiotic.

RUSSELL J. BLATTNER.

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# News and Notes

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The American Board of Pediatrics, Inc., announces the following dates for examination:

Written: Under local Monitors Friday, June 24, 1949.

Oral: Cleveland, Ohio, Sept. 16, 17, and 18, 1949.

New York City, Oct. 21, 22, and 23, 1949.

Chicago, Ill., Dec. 9, 10, and 11, 1949.

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Dr. Henry W. Titus of New Rochelle, N. Y., died March 17, 1949. Dr. Titus had recently retired after forty years of pediatric practice. He was formerly head of the pediatric service at the Grasslands Hospital.

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Dr. James H. McKee of Philadelphia died March 25, 1949.

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Dr. E. J. Huenekens, clinical professor of pediatrics at the University of Minnesota, has been appointed national medical director of the Kenny Foundation.

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Dr. Harold K. Faber of San Francisco, professor of pediatrics and head of the department at Stanford University School of Medicine, will retire Sept. 1, 1949, and become professor emeritus. Dr. John A. Anderson, professor of pediatrics at the University of Utah, College of Medicine, Salt Lake City, will succeed Dr. Faber as professor of pediatrics at Stanford.

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The National Foundation for Infantile Paralysis has issued the following "Message to Parents" for the 1949 season in case polio becomes epidemic in an area:

Avoid crowds and new contacts in trains, buses, or boats, if possible; avoid crowded places where you may be close to another's breath or cough.

Avoid over-fatigue; too active play, late hours, worry, irregular living schedules may invite a more serious form of the disease.

Avoid swimming in water which has not been declared safe by your health department.

Avoid chilling. Take off wet clothes and shoes at once. Keep dry shoes, sweaters, blankets, and coats handy for sudden weather changes.

Keep clean. Wash hands after going to toilet and before eating. Keep food covered and free from flies and other insects. Burn or bury garbage not tightly covered. Avoid using another's pencil, handkerchief, utensil, or food touched by soiled hands.

Call your doctor at once if there are symptoms of headache, nausea, upset stomach, muscle soreness or stiffness, or unexplained fever.

Consult your Chapter of the National Foundation for Infantile Paralysis for help. Your Chapter (see local telephone book or health department for address) is prepared to pay that part of the cost of care and treatment you cannot meet—including transportation, after-care and such aids as wheel chairs, braces, and other orthopedic equipment. This service is made possible by the March of Dimes.

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A sound film in color has been produced at the University of Chicago on "The Function of the Ear in Health and Disease." It is edited by Drs. H. G. Kobrak, Joseph E. Hind, and Robert B. Miller. The film demonstrates the response of the ear to sound in health and disease, pathology, hearing curves in deafness, etc. It is available to universities and professional groups without charge through the Auralgan Research Division, 100 Varick St., New York 13, N. Y.

## Book Reviews

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**The Thyroid and Its Diseases.** J. H. Means, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital, Boston, ed. 2, Philadelphia, 1948, J. B. Lippincott Co., 559 pages. Cloth, price \$12.00.

Eleven years ago the first edition of this book was generally accepted as the most comprehensive monograph available on the "Thyroid and Its Diseases," although the authors made no such claims as to its completeness. In the Preface of the first edition, the simple statement was made that "It is an account of the personal experiences of a considerable group of workers in a single thyroid clinic and of the opinions and convictions derived from this experience." The clinic was that of the Massachusetts General Hospital. In the intervening period of time the scope of this clinic has been broadened considerably by growth of personnel, liaisons with other clinics and institutions, and the contributions of competent workers from other countries who have spent appreciable periods of time at work in association with the clinic.

The second edition of this book again presents an excellent and comprehensive monograph on the subject of the thyroid gland. The general plan of the book is unchanged. Approximately the first third is again devoted to a review of the anatomy, nerve supply, biochemistry, physiology, and pathology of the thyroid, emphasizing the additional points of knowledge and suggestions derived from continued investigations, particularly with the use of the newer "tools" such as uptake of radioactive iodine and antithyroid drugs (thiocyanate, thiouracil, etc.). The chapter on Pathology of the Thyroid has been written by Rulon W. Rawson, M.D., Assistant Professor of Medicine, Harvard University. The interrelationship of the thyroid to other endocrine glands and to the body in general is stressed. The theory of the "thyroid-axis" is further supported and the site of the action of various therapeutic measures is explained on this theory. In the chapter on Methods of Examination in Thyroid Cases, attention is drawn to the history of goiterogenic foods and drugs, and the value of such diagnostic procedures as creatine tolerance, protein-bound iodine determinations, collection of radioactive iodine by the thyroid, and periodic bone-age determinations (in children). The measurement of the basal metabolic rate and blood cholesterol is, of course, included. The authors have altered somewhat their classification of disorders of the thyroid. The chapters on myxedema have been changed very little. The differentiation of primary thyroïdal myxedema and anterior-pituitary myxedema (Simmonds' disease) is pointed out. Of special interest to the pediatrician is the importance, from a prognostic point of view, of the careful differentiation of the true cretin from the juvenile myxedema patient. The chapter on Graves' disease (thyrotoxicosis—old classification) contains adequate discussion of the newer types of therapy, such as antithyroid drugs and radioactive iodine, in addition to the established methods of surgery and iodine administration. Psychic trauma is ascribed only the "trigger" role in Graves' disease. The authors do not commit themselves to any fixed preference for a therapeutic measure, but wisely state: "At the present time, treatment must be individualized, and in each case the doctor must add the pros and cons of each type of treatment and decide which offers most to his patient."

The chapters on Tumors of the Thyroid, Thyroiditis, Anomalies of the Thyroid, Hypometabolism Without Myxedema, and Thyroid Administration in Diseases of Other Than Thyroid Origin, have been somewhat rearranged and brought up to date. The chapter on The Surgery of the Thyroid has been rewritten by Oliver Cope, M.D., Assistant Professor of Surgery, Harvard University.

L. D. THOMPSON.

Parent and Child. Catherine Mackenzie, New York, 1949, William Sloane Associates, Inc.

This book is a compendium of the articles written for the *New York Times* by an able and sincere journalist in the field of child-parent relationships. There is a difficulty, largely inherent in the enormity of the subject matter, which necessitates quoting isolated remarks from a multitude of authors. In the compact book form, this leaves the reader gasping a bit and one wonders whether it might not be less bewildering to parents if they were not confronted with quite such a parade of names. However, it is to Miss Mackenzie's credit that she is refreshingly honest in giving credit where it is due. She does not presume to give advice according to any preconceived ideas but reports the new developments in the field judiciously. The language is simple and forthright without being condescending. In spite of its local New York coloring, it is a book which parents all over the country will find useful.

M. E. BRANSCOM.

Maternity in Great Britain. London and New York, 1949, Oxford University Press, 252 pages. Price \$4.00.

The report of a survey of the social and economic aspects of pregnancy and child birth undertaken by a Joint Committee of the Royal College of Obstetricians and Gynecologists and the Population Investigation Committee. This is a thorough, well-interpreted report of more interest to the obstetricians than the pediatricians. Conditions surrounding obstetrical care in Great Britain, where the midwife plays such an important role, are so different from practices in the United States that the report is more of interest than of value to American practitioners and students of sociology.

The Normal Child. Alan Brown, M.D., and Elizabeth C. Robertson, M.D., ed. 4, Toronto, 1949, McClelland and Stewart, Ltd., 274 pages. Price \$3.00.

This is the fourth edition of Dr. Brown's book for mothers on the care of the baby and child. It has been entirely rewritten since the third edition which was published in 1932. It follows the general format of the many books on the subject. The text is clear and the revised edition is in keeping with modern practice and thought.

The Ciba Collection of Medical Illustrations. Summit, N. J., 1949, Ciba Pharmaceutical Products, Inc., 224 pages. Price \$6.50.

For a number of years the Ciba Company has published and issued loose-leaf colored illustrations of anatomy and pathology by Frank H. Netter, M.D. One hundred ninety-one of these color plates have been bound together and are available at cost of printing. It is an excellent, well-printed book and the colored illustrations by Dr. Netter are far above average.

Current Therapy 1949. Edited by Howard F. Conn, M.D., Philadelphia, W. B. Saunders Company, 672 pages. Price \$10.00.

This book on the "Latest Approved Methods of Treatment for the Practicing Physician" is a decidedly unique and interesting text. With an editorial-consulting group of twelve well-known medical teachers, over 200 physicians have contributed articles detailing the specific treatment of some 300 conditions. The text is confined to treatment and in some instances two or more authors have contributed methods for the same condition. The text is divided into fourteen sections as (1) the infectious diseases, (2) diseases of the digestive system, (3) diseases of metabolism, and so on, and includes dermatology, allergy, and obstetric and gynecologic conditions. The text is clear and printed in large type, making it easy to read. As nearly all of the methods have been contributed by men nationally looked upon as authorities in their special fields, the book should be of great value to the busy practitioner. The text, however, does not include many of the pediatric conditions which form such a large part of the practice of the general practitioner.

## Editor's Column

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### FEDERAL AID FOR MEDICAL EDUCATION

IN VIEW of the controversy which has arisen over the question of Federal aid for pediatric education, it is pertinent to point out that the Federal government is allotting some twenty million dollars to medical teaching institutions for the fiscal year ending June 30, 1949. The bulk of this is for what is essentially graduate and postgraduate education.

In an address at the recent educational meetings in Chicago on February 7, Surgeon General Scheele of the Public Health Service stated that for the current fiscal year the Service had available a total of \$24,427,000 to aid medical research and education. This expenditure is limited to certain specific fields of which cancer and psychiatry are examples. About eleven million dollars has been invested in research grants, eight million in construction grants, three million in fellowships and traineeships, and a little over two and one-quarter million in teaching grants. Grants for undergraduate teaching in cancer have been made to medical and dental schools. The March 12 issue of the *Journal of the American Medical Association* announced the allotment of \$1,500,000 to forty-two medical schools for undergraduate teaching in psychiatry. Most of the schools will receive \$12,500 a year for three years beginning July 1, 1949. Dr. Scheele stated that about 84 per cent of the total funds available for research and training has gone to teaching institutions. In addition to these funds, other sums have been allotted through the Children's Bureau to the medical schools for research and graduate training programs in maternal and child health. Thus the use of Federal funds for medical education is not a matter of ideological controversy but an accomplished fact. Let us say further that although we have been keeping an ear close to the ground, we have heard of no complaints of dictation of education policies by the government bureaus in the allotment of these grants.

The point we would like to raise is that although in a broad sense all this money is for medical education, as medical knowledge is dependent upon research, most of the money is being spent on the superstructure when the soundness of a program depends on the strength of its foundation. The foundation of medical education is the undergraduate teaching in the medical school, and this, from a financial standpoint, is the weak point in medical education today. Unless undergraduate education is sound, graduate and postgraduate programs of education and research based on Federal funds will inevitably fail in part to meet their objectives.

In the recently published survey of pediatric education which was reviewed in last month's issue of THE JOURNAL, Dr. John Mitchell presented some very illuminating figures in regard to undergraduate teaching as a whole and budgets for pediatric teaching. In twenty-five schools the budget for pediatrics is less than \$50 per student, in twenty-five, between \$50 and \$200, and in twenty-five,



over \$200. In forty-three schools the amount is less than \$100 per student and in twenty-seven over \$100. In five schools it is less than \$10 per student per year, and in four, over \$400.

The question that arises is why should there be such violent opposition on the part of some to Federal aid for undergraduate education when there is seemingly no opposition to the Federal government allotting about twenty million dollars this fiscal year to the teaching institutions for graduate and postgraduate education. It has nothing to do with the controversial subject of medical socialization, but is purely concerned with ways and means of improving medical care, which, in the final analysis, depends upon medical education. In much of the rather emotional discussion of medical care and economics which has taken place in recent months, the fact that good medical care is more dependent on the education and skill of the doctor than on the way in which he is remunerated for his services has been completely ignored by many taking part in the discussion.

The one and one-half million dollars recently allotted for undergraduate teaching in psychiatry went to only forty-two of the seventy medical schools. The basis of selection was where it was most needed and where it would do the most good. A similar sum for undergraduate pediatric teaching, divided among the schools which the survey has shown have inadequate budgets for good pediatric teaching, would be a sound investment for the children of the nation.

B. S. V.

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#### STREET AND HIGHWAY ACCIDENTS IN 1948

THERE were 32,200 persons killed on the streets and highways in 1948. This is a decrease of 300 under 1947 but the number of nonfatal injuries reported jumped from 1,365,000 to 1,471,000. Of the 22,700 deaths resulting from the actions of drivers, 10,080 (44.4 per cent) were attributed to speeding. Of the deaths, 3,530 were in children under 14 years of age, a decrease of nearly 500 under 1947. Of the fatal accidents, 85.5 per cent occurred when the weather was clear, and 78.7 per cent when the roads were dry. Over one-fourth of the fatal accidents occurred in the late afternoon and early evening hours, 4 to 8 P.M. Saturday and Sunday were as usual the days with the highest rates and account for approximately 40 per cent of the total number of persons killed.

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## Original Communications

### FIBROSIS OF THE PANCREAS IN INFANTS AND CHILDREN

#### AN ILLUSTRATED REVIEW OF CERTAIN CLINICAL FEATURES WITH SPECIAL EMPHASIS ON THE PULMONARY AND CARDIAC ASPECTS

CHARLES D. MAY, M.D., AND CHARLES UPTON LOWE, M.D.  
MINNEAPOLIS, MINN.

THERE has been a tendency in descriptions of fibrosis of the pancreas to select certain combinations of manifestations and proclaim corresponding "types" of the disease.<sup>9, 12</sup> Consequently one hears surprise expressed when a patient is encountered who cannot be fitted neatly into one of these abstract types. The many natural variations in symptoms demand a more dynamic concept of this disease. Then the less commonly appearing combinations of symptoms will take their place as understandable variations in a coherent, basic process. All the fluctuations in respiratory symptoms, variations in the feces, and contrasting degrees of nutritional disturbances are the result of different systems being affected simultaneously and continuously but with independently varying intensity.

It is our intention to portray the interplay of certain aspects of the disease as they may appear in different age periods and at various times in the same patient. Much of the evidence supporting this point of view has appeared in previous reports.<sup>6, 14, 16, 18, 22, 26, 28, 29</sup> This is augmented herein by a series of illustrative figures and further clinical descriptions derived from 134 patients whom we have studied. A bibliography of selected papers is appended for reference and as a guide in obtaining a more complete knowledge of the disease.

The name generally employed for this disease, "cystic fibrosis of the pancreas," is misleading because: (1) it focuses attention on one aspect, perhaps the least vital, of the disease, no hint being made of the constant lesion in the lungs although this aspect of the disease appears to be the most important one in determining the clinical course and the fate of the victim; (2) no suggestion of the variability of the symptoms is revealed through the fixed lesion of the pancreas; (3) this terminology has served to overemphasize the nutritional problem and the role of diet in the treatment of the disease. Although the theory of pathogenesis advanced by Farber and Wolbach (generalized alteration in mucous secretions leading to obstruction, dilatation, atrophy, and fibrosis of secreting glands) is an intriguing, unifying concept,<sup>2, 18</sup> it is not sufficiently established to justify adopting the proposed name "mucoviscidosis."<sup>10</sup> Fibrosis

Many of the studies forming the basis of this paper were aided by a grant from Mead, Johnson & Company; from the Department of Pediatrics, Harvard Medical School, Boston, Mass., and from the Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minn.

of the pancreas, the term we employ, at least has the merit of being noncommittal and containing no factual error.

At the outset it must be clear that we are dealing here only with the fully developed disease, fibrosis of the pancreas. By this we mean that other forms of pancreatic insufficiency, such as that due to atresia of the pancreatic duct, are not of concern to us at present.

It is conceivable that all grades of severity of altered secretions might exist, from minimal microscopic changes, which could hardly cause symptoms, up to the more profound and widespread changes that cannot but produce symptoms. Actually we have never encountered any confusion clinically. We have never recognized any minimal or subclinical stages of the disease, primarily because symptoms are not produced until the involvement in the pancreas and lungs has become advanced and widespread. Whenever a patient has been shown to have this disease, even when examined so early that symptoms were very mild, we have found the pancreatic enzymes to be virtually absent from the duodenum and the lungs already clearly abnormal as demonstrated by clinical or roentgenographic examination. Other organs or systems have given no symptoms unless they have been severely affected. It appears to us that there is a wide gap between the minimal findings on microscopic examination discovered in patients dying of some disease other than fibrosis of the pancreas and the unequivocal pathologic changes which are invariably found in those dying with all the clinical manifestations of fibrosis of the pancreas.

There is need for better evidence that the basic pathologic process may appear in all stages of development at any age, before or after birth. All the clinical evidence is for a process appearing just before, at, or shortly after birth with rapid progression to full development with symptoms promptly produced.

#### MECONIUM ILEUS

Meconium ileus is the least complicated exhibition of the underlying process. As early as 1905 Landsteiner,<sup>1</sup> because of a lesion which he demonstrated in the pancreas, suggested that intestinal obstruction in the newborn infant from inspissated meconium might be dependent on absence of pancreatic secretion. Others found the same alteration in meconium with simple atresia of the pancreatic duct.<sup>20, 21</sup> In the majority of infants with meconium ileus, a lesion indistinguishable from that occurring in infants with fibrosis of the pancreas who never had meconium ileus has been found in the pancreas.<sup>22</sup>

Meconium ileus is a disease of full-term infants. In our experience, premature infants have not been affected. Meconium sufficiently inspissated to obstruct the intestine would seem to be a sign that the pancreatic lesion is so advanced that no appreciable pancreatic secretion reaches the intestine. Only twenty-nine of our 134 patients with fibrosis of the pancreas developed meconium ileus.<sup>23</sup> This would indicate that the lesion develops rapidly near term but may not reach its full extent until after the meconium is passed.

The final link in relating meconium ileus to fibrosis of the pancreas was provided by success in relieving the intestinal obstruction and maintaining survival long enough for the telltale pulmonary lesions to fully develop. Four patients illustrate this sequence of events. One was born with meconium ileus.

The obstruction was relieved by surgery and enteral irrigations with pancreatin. By intensive administration of fluid and other supportive therapy, he survived with an ileostomy. During the ensuing weeks, he developed classical clinical and roentgenologic signs of the pulmonary lesion, and was found to have no trypsin in his duodenal secretions. He is still alive and represents an unmistakable example of true fibrosis of the pancreas of the sort regularly encountered that usually escapes meconium ileus. Two other patients who endured an identical sequence of events for two and six months, respectively, gradually acquired definite clinical signs of the disease (Plate XII). At necropsy all the usual findings in the lungs and pancreas were found to be present in these cases.

The link between meconium ileus and fibrosis of the pancreas is further illustrated by a boy, now 6 years old, who had signs of intestinal obstruction at birth and who fortunately was relieved of obviously inspissated meconium by rectal irrigations with pancreatin solution.<sup>26</sup> FIG. 9 After a brief period of "wheezing" he was free of pulmonary signs but developed grossly fatty stools and was treated for celiac disease for four years without satisfactory response. Then his ravenous appetite and foul stools were correlated with the neonatal history and five examinations of his duodenal secretions over a two-year period revealed no tryptic activity. Furthermore, his lungs now show definite roentgenographic findings such as we have seen in other children with fibrosis of the pancreas who have relatively quiescent chronic pulmonary disease. He also has a chronic sinus infection with *Staphylococcus aureus* which produces extraordinarily viscid mucoid secretions.

Many of the children with fibrosis of the pancreas who did not have intestinal obstruction at birth, may nevertheless have had alterations in the viscosity of their meconium proportional to the degree of pancreatic failure. All gradations of difficulty in passing meconium during the neonatal period may be anticipated in such cases. The subsequent course of patients with inspissated meconium or meconium ileus tends to follow the sequences illustrated by this sample group. However, there is not a clear-cut "type" of patient surviving meconium ileus apart from or different from the group with fibrosis of the pancreas.

All infants suffering from meconium ileus or unusual difficulty in passing meconium ought to be suspected of fibrosis of the pancreas. If relieved of intestinal obstruction, they should have the pancreatic enzymes assayed and observed in the following months with due regard for the possibility of development of the pulmonary lesion. Rarely a child will turn out to have congenital atresia of the pancreatic duct or other pathology of the pancreas without developing pulmonary lesions. Quantitative information as to the composition of meconium in pancreatic insufficiency is lacking. This might be of value in distinguishing inspissation from this cause from variation of normal meconium which might be viscid enough to cause confusing symptoms.

#### THE PANCREATIC LESION

It may be deduced from the information already given that the clinical evidence strongly suggests (1) that the lesion in the pancreas develops early, just prior to, at, or soon after birth; (2) that it must progress rapidly to loss of function of the exocrine portion of the pancreas; and (3) that once fully de-

veloped, it is irreversible, repair and recovery not occurring; the damage is complete and final. It is well known that clinical symptoms would not be expected unless this were true, for very little normal pancreas would suffice to carry out its usual function in digestion. This has been proved experimentally in animals and by patients who have undergone subtotal pancreatectomy. In one such patient in our experience, the concentration of pancreatic enzymes in the duodenum hardly reflected the loss of approximately nine-tenths of the pancreas, the absorption of nitrogen and fat were unimpaired, and the nutrition was unaffected.

We have found on analysis of our clinical data<sup>33</sup> that, besides the patients with meconium ileus, others with fibrosis of the pancreas develop symptoms of pancreatic insufficiency soon after birth. One-third have abnormal stools from birth. Many fail to gain weight in the first weeks of life in spite of abundant intake of food and inconspicuous pulmonary symptoms. Fully two-thirds show one or another symptom of pancreatic insufficiency by the age of 4 weeks. That no return of pancreatic function occurs, once it is destroyed, has been demonstrated in our patients again and again throughout long periods with repeated duodenal enzyme analyses (over a period of six years in one patient). This evidence for lack of pancreatic enzymes and the irreversibility of the pancreatic lesions has been abundantly verified by clinical observations and metabolic balance studies.<sup>14-17</sup>

It is obvious then that the contribution pancreatic insufficiency makes to the total clinical appearances in this disorder ought to be a constant one. The variability in the features of the disease must be dependent on other factors.

One consideration which might lead to an *apparent* variability in the consequences of complete pancreatic insufficiency is an extraordinary adaptation which the body can make to the lack of pancreatic enzymes. It has been shown that the absorption of both fat and protein frequently can be 60 per cent or more of normal without the aid of pancreatic enzymes.<sup>14-17</sup> This adaptation may take time to develop and the degree of adaptation may be variable so that fluctuations in the efficiency of digestion and in symptoms might be expected to occur. The "plateau" period of failure to gain weight, frequently observed during the first three months of life,<sup>26</sup> may be explicable on such a basis.

A fortunate feature in this disorder is the preservation of a good appetite or the development of a really ravenous one. This leads to excellent or increased intake of food and compensates more or less for the inefficient digestion. If there is no extra burden to carry such as infection or severe pulmonary lesions, normal nutrition is frequently maintained. In fact, patients with this disease who follow their instinct, uninhibited by medical care, and consume large quantities of well-balanced diets, often maintain themselves in excellent nutrition. This led to questioning the value of dietary restrictions and to concentrating attention on the pulmonary process.<sup>26</sup> It is noteworthy that maintenance of good nutrition does not prevent the ultimate appearance of characteristic pulmonary symptoms, often even in a severe form.

The ravenous appetite, inefficient digestion compensated for by increased intake of ordinary foods, and ability to maintain good health for long periods without pancreatic enzymes had been observed in experimental animals before this disease was described.<sup>13</sup> It should be recalled, however, that such animals,

free of pulmonary disease, often exhibited mysterious slumps in their appetite, food intake, and weight gain. It has not been possible to disentangle such a phenomenon in our patients from the other more obvious causes of decline such as those attributable to the pulmonary process.

The clinical evidence of the pancreatic lesion is found in the feces. The most dependable sign is increased bulk and weight of feces. Impairment of digestion cannot but lead to increased fecal excretion. Commonly, mothers and even doctors and nurses state that the feces of a patient with fibrosis of the pancreas appear normal. Ordinarily, what is meant is that the feces are formed, not fatty or foul, and individual specimens are not unduly large. But were the output of feces of an entire day to be seen, or the increased number of formed stools noted, it would be evident that the total fecal excretion is always greater than normal. Although a specimen of the feces may be formed, and not abnormally large, it is much more usual for the feces to be abnormal in appearance. The stools are sometimes unformed but not frequent, which condition can easily be confused with chronic diarrhea. Rarely they are numerous and loose. Initially they do not often appear fatty. Beyond the first year of life they are frequently fatty and pale as well as bulky, mushy, and foul. Sometimes actual drops of fat separate from the feces. During certain periods, according to the diet perhaps, the stools may be frothy and irritating to the buttocks, leading to an erroneous diagnosis of "carbohydrate intolerance." In the same patient any of the various appearances of the feces may predominate from time to time: all are equally "characteristic" none is diagnostic, but all are seen in many forms of chronic intestinal insufficiency. A rare patient consistently passes stools so normal in appearance that only total weight or metabolic balance study reveals the extent of the fecal wastage of undigested food. Ample opportunity for this great variety in the appearance of the feces is allowed by differences in age of the patients, types of diet, fluctuations in absorption, along with the variable burden provided by the pulmonary lesion.

It may be pointed out that the impairment of absorption of fat particularly affects the fat-soluble vitamins. Normal levels of vitamin A in the blood, and presumably also of vitamin D, have always been maintained by simply increasing the oral dose of these fat-soluble vitamins to approximately three times normal amounts. According to the results of recent studies of the absorption of emulsified forms of the fat-soluble vitamins,<sup>23, 24</sup> the selection of a more dependable means of administering these substances to patients with impaired absorption of lipids may be possible. Parenteral injection of fat-soluble vitamins is both unnecessary and unwise. If the impaired absorption is not compensated for by increasing intake, deficiency may occur. In fact, all of the examples of deficiency of vitamin A which we have recognized clinically or pathologically resulted from failure to provide even ordinary amounts of supplementary vitamin A.<sup>6</sup> Rickets has occurred only once in our experience, more because of the retardation in growth, perhaps, than because of deficiency vitamin D has not occurred. Undercalcification of the bones is found almost regularly.

Thus, even the various consequences of the fixed lesion in the pancreas can only be encompassed by a dynamic concept interrelating the insufficiency of external secretion of the pancreas with the other aspects of the disease.

This sort of understanding makes practical management more rational and appropriate. The diet may as well be a well-balanced one given to satisfy the appetite. The usefulness of pancreatin is questionable because of its low or uncertain enzyme potency, expense, and the relatively little improvement effected in absorption. It frequently lessens appetite and undermines this compensatory mechanism. A better enzyme product for substitution therapy would be desirable. The feces are a reliable, but not diagnostic, sign of the disease, requiring close scrutiny for correct evaluation. Little hope can be offered for ultimate elimination of the pathology in the pancreas. Fortunately the course and fate of the patient are determined more by other factors which may be reversible, mild, or more successfully controlled. There is no evidence that the severity of the pulmonary process is in any way directly dependent upon the severity of the pancreatic lesion.

#### THE PULMONARY LESION

It seems desirable to give a somewhat more extensive consideration to the pulmonary lesion accompanying fibrosis of the pancreas because descriptions in the literature are fragmentary and scattered. A comprehensive picture of the course and significance of the pulmonary process is necessary for accurate diagnosis, proper management, and sound prognosis. Only by a full appreciation of the dynamic interplay between the variable components forming the lesion in the lungs can one understand the wide gamut and smooth gradation of the clinical manifestations.

On pathologic examination<sup>18</sup> of the lungs an unusually viscid mucopurulent secretion is seen exuding from the bronchi. Microscopically the bronchioles are found plugged with a mixture of homogeneous mucus and purulent exudate. There are varying degrees of inflammatory response usually limited to the peribronchial region, occasionally leading to areas of alveolar consolidation, but more commonly to bronchiolectasis or scattered small abscesses. The lung parenchyma is affected primarily with the emphysema and atelectasis which are the inevitable result of bronchiolar obstruction. Interstitial fibrosis is usually not conspicuous. Infection with *Staph. aureus* is regularly present. The type of infection is unique in the infant age period in that the invasiveness characteristic of the *Staph aureus* is not apparent and the systemic response is very subtle. But, in spite of this indolence, the infection is remarkably persistent. Whether the pathology in the lungs is due to this infection, to elaboration of an unusually thick mucoid secretion by the bronchial glands, or, as seems possible, to a combination of both, cannot be regarded as settled.

Patients who die of meconium ileus, having survived but a day or two, may not show characteristic pathology in the lungs, but all such patients who have lived longer have abnormal lungs (vide supra). Only three patients with fibrosis of the pancreas have been encountered by us who were essentially free of pulmonary complaints. In each case roentgenograms of the lungs revealed minimal peribronchial infiltration and emphysema. Thus it appears that the pulmonary lesion is a regular accompaniment of the pancreatic lesion and has its inception simultaneously with it.

The clinical signs and symptoms are clearly referable to variation in the severity of the different elements in the pathology. A consideration of the accompanying photographs and their legends in the order arranged (Plates I-XII) allows one to pass from an illustration of the simplest pulmonary involvement to increasingly complex and varied manifestations of disease in the chest. This approach provides an array of the clinical phenomena likely to be encountered. A clear conception of the basis of these manifestations may be facilitated by the text which follows.

Clinical signs and symptoms include wheezing, dyspnea, cough, the production of sputum composed of tenacious, mucoid substance or a thick, mucopurulent material, cyanosis sometimes associated with clubbing of fingers and toes, fever, and deformity of the chest. These occur in various combinations to provide the appearances which are seen in the various phases of the disease. During the neonatal period, wheezing or dyspnea may be noted without other symptoms or signs. Three instances of pathology in the lungs without clinical symptoms have already been mentioned. Cough is usually a prominent symptom before 6 months of age and frequently dates from birth. When the disease is progressive, dyspnea increases until cyanosis finally appears, often as early as 2 to 5 months of age. One-fourth of our patients developed cyanosis at some time. At the onset of dyspnea in the infant retraction of the intercostal spaces is common, but if the process continues severe the thoracic cage assumes a barrel shape in later months and years. Sooner or later in the great majority of patients a respiratory infection is contracted, and in its wake there remains a chronic pulmonary infection with *Staph aureus*. Whereas before, occasionally a scanty clear viscid sputum had been observable in the pharynx on coughing, after the infection is established, a viscid, mucopurulent, yellow or green, often copious, sputum is seen or may be expectorated by the older child. The *S. aureus* is so regularly and predominantly the infecting organism that it almost bears the role of a stigma of the disease. At this point, while a slight fever may be present, there usually is none and the systemic reaction is more one of insidious decline in the total physical and nutritional condition of the patient than of an overwhelming reaction.

As these signs and symptoms are described, one might gain the impression there is an ominous march of events toward inevitable doom. Quite to the contrary, the progression may halt at any point and even be reversed to an improved or even symptomless state. In fact, seven of our patients even lost their cyanosis as they improved.

Findings on physical examination are variable, depending on degree of bronchiolar obstruction, character of the exudate, extent of the process, and occurrence of infection. There may be gradual fluctuation in the signs but at times the change from one phase to another is so rapid as to suggest that there may be an element of muscular spasm about the involved bronchioles. Proof of spasm is scanty, but suggestive responses to antispasmodic agents have occasionally been observed. The outstanding findings are those of emphysema: diminished tidal exchange, distant vesicular breath sounds, resonance, and hyperresonance. Atelectasis is not often massive enough to give definite signs such as dullness or bronchial breathing but is usually a roentgenographic or micro-



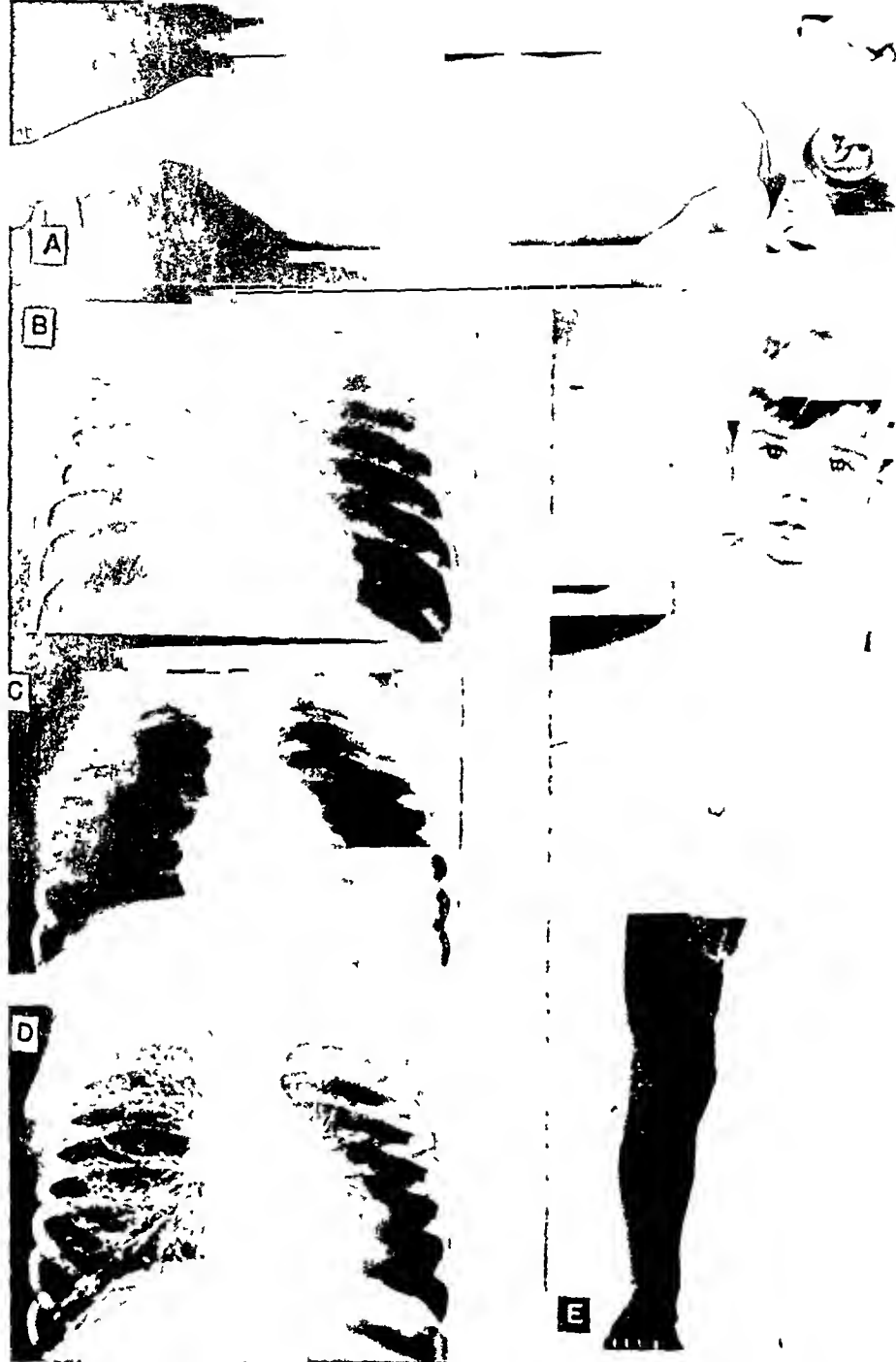


PLATE I—J. N. 1. Patient at 6 months. B, Lungs at 6 months. C, Lungs at 2 years, 2 months. D, Bronchogram at 2 years, 2 months. E, Patient at 2 years, 2 months.

Fibrosis of the pancreas can exist with but minimal pulmonary complaints. This undoubtedly was due to mild and intermittent bronchiolar obstruction. Possibly there was some element of smooth muscle spasm, but evidence of infection was lacking. Nutritional state was excellent both at 6 months and at 2 years. Roentgenograms show minimal peribronchial infiltration early and moderate emphysema later. Lipiodol bronchograms revealed no bronchiectasis.



PLATE II.—L. G., A, Lungs at 2 years, 8 months. B, Patient at 2 years, 8 months old. Moderate peribronchovascular infection, when superimposed upon the existing basic pathology of altered secretions, may very early cause a decrease in weight gain and growth. This patient had periods of exacerbation of her pulmonary infection during which weight gain was poor. At these times evidence of parenchymal disease was obvious by physical examination and x-ray. During interim periods weight gain was good and evidence of disease was lacking. This x-ray taken during a quiescent period demonstrates slight emphysema and moderate peribronchovascular infiltration. At this time minimal clubbing of the fingers was first noted.

C. D., C, Lungs at 1 year, 10 months. D, Bronchogram at 2 years, 11 months.

Most children with mild pulmonary infections have periods of improvement and periods of increased disease. The child whose chest is shown by roentgenogram above had these periods but retained an area of constant infection in the right lower lobe. This was more apparent on physical examination than by x-ray since râles were always present here.

The early x-ray demonstrates a common concomitant of bronchiolar obstruction; atelectasis. This is almost always patchy in distribution and seems to be at least in part related to the infection which is superimposed upon the altered secretions. Certainly it is related to obstruction of smaller bronchi and bronchioles. This is best shown by the fact that when the infection improves much of the atelectasis disappears. The bronchogram at 2 years, 2 months demonstrates poor filling in the right lower lobe bronchus. Diminution of atelectasis and the appearance of moderately severe emphysema may also be seen.

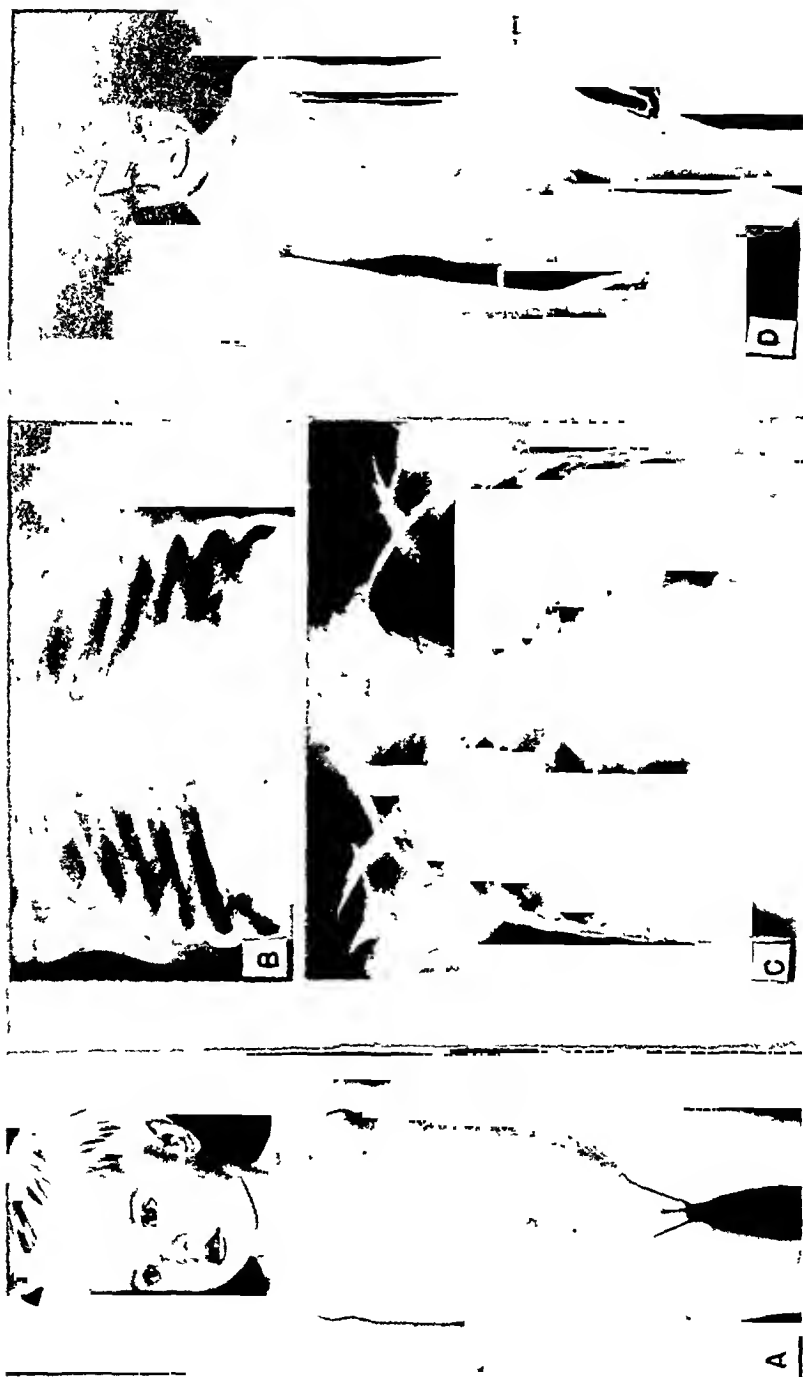


PLATE III.—B. II. A, Patient at 1 year, 5 months. B, Lungs at 1 year, 5 months. C, Lungs at 8 years. D, Patient at 8 years. Sometimes patients who have moderate pulmonary disease in early childhood may survive with little or no therapy and grow remarkably well. Undoubtedly, the basic pulmonary pathology remains, but bronchiolar obstruction is minimal and infection mild. This child was followed for six and one-half years. Physical examination at 8 years of age revealed no pulmonary abnormalities, but the roentgenogram of the chest showed mild emphysema and minimal peribronchial infiltration.

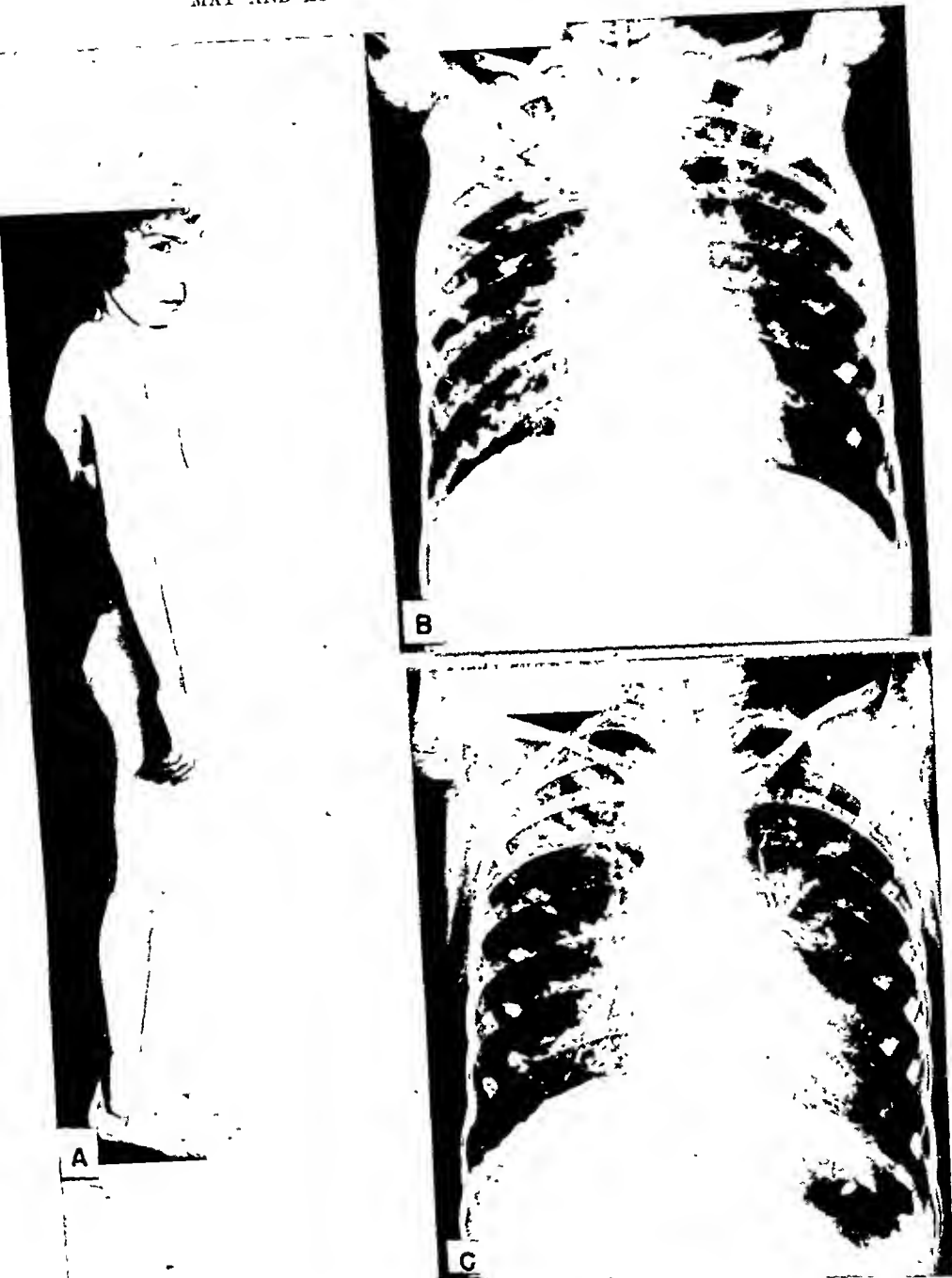
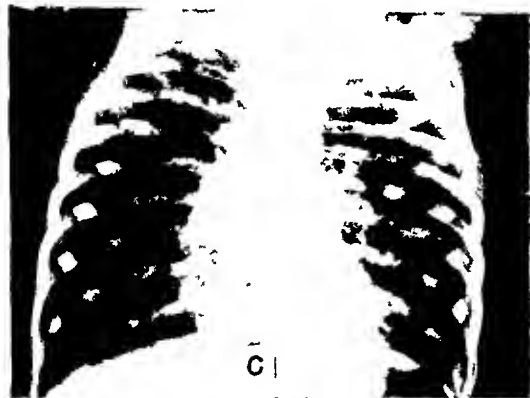


PLATE IV.—J. F., A, Patient at 8 years. B, Lungs at 7 years, 10 months. C, Bronchogram at 7 years, 10 months.

Apparently children can survive long periods with even severe pulmonary disease. This child was first seen at 8 years of age, never having had pulmonary complaints severe enough to demand the attention of a physician. She had obviously severe disease both by x-ray and on physical examination, and clubbing of the fingers was marked. The roentgenogram revealed scattered atelectasis and emphysema, peribronchial infiltration and patchy pneumonic consolidation. Lipiodol bronchograms showed extensive bronchiectasis, one of the few cases encountered in the group of living children.



PIATR V—N. R. A, Patient at 1 year, 7 months. B, Lungs at 1 year, 2 months. C, Lungs at 2 years, 5 months. D, Patient at 2 years, 5 months.

If the areas of infection persist, the periods of remission become less frequent and the exacerbations more severe, nutritional state suffers, and the patient becomes more obviously wasted. This child failed steadily and within ten months became marasmic and died. His x-rays show progress of both peribronchial infiltration and emphysema and an increase in the areas of atelectasis and focal pneumonitis.



PLATE VI—M. C. A. Patient at 1 year, 10 months. B, Lungs at 1 year, 3 months. C, Lungs at 1 year, 10 months. D, Lungs at 2 years.

Adequate nutrition and a mild pulmonary lesion early in life is no promise of a benign clinical course. This child was robust and active when first seen with what was thought to be a mild right lower lobe pneumonia. The diagnosis of fibrosis of the pancreas was not even suspected. Seven months later she still had adequate subcutaneous tissue but her chest was severely diseased. Peribronchial infiltration, patchy atelectasis and emphysema were all marked. Within two months she was dead. The chest X-ray taken just before death illustrates the remarkable rapidity with which the disease progressed.

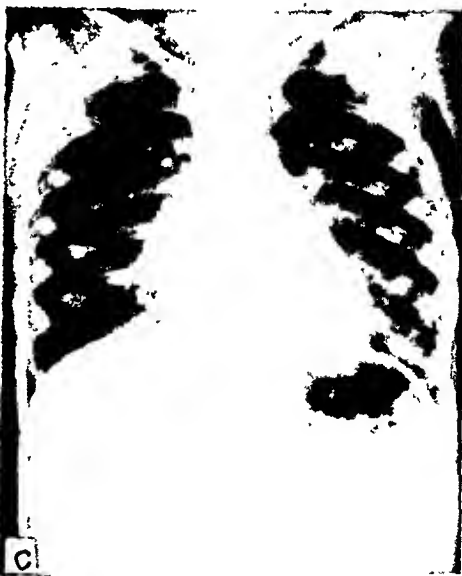


PLATE VII.—D. C. A, Lungs at 2 years, 2 months. The pneumonitis at times can reach extraordinary degrees of severity. It is, however, superimposed upon the basic pathology and although this roentgenogram shows extremely severe pneumonia on the right, the left chest shows the expected peribronchial infiltration, patchy atelectasis, and emphysema.

There is a curious host-parasite relationship between the *Staph. aureus* and patients with fibrosis of the pancreas. Only rarely do these children show the expected complications of pulmonary infection with this organism, in spite of the fact that it is almost uniformly present. Septicemia, abscess formation, and empyema are very rare. Two children have been seen with empyema. One of these died (D. M.). B, lungs at 3 months. The other survived and two months later was growing well (M. B.). C, lungs at 2 years, 10 months, eighteen months after empyema resolved. His chest roentgenogram is not normal but physical examination is not remarkable.

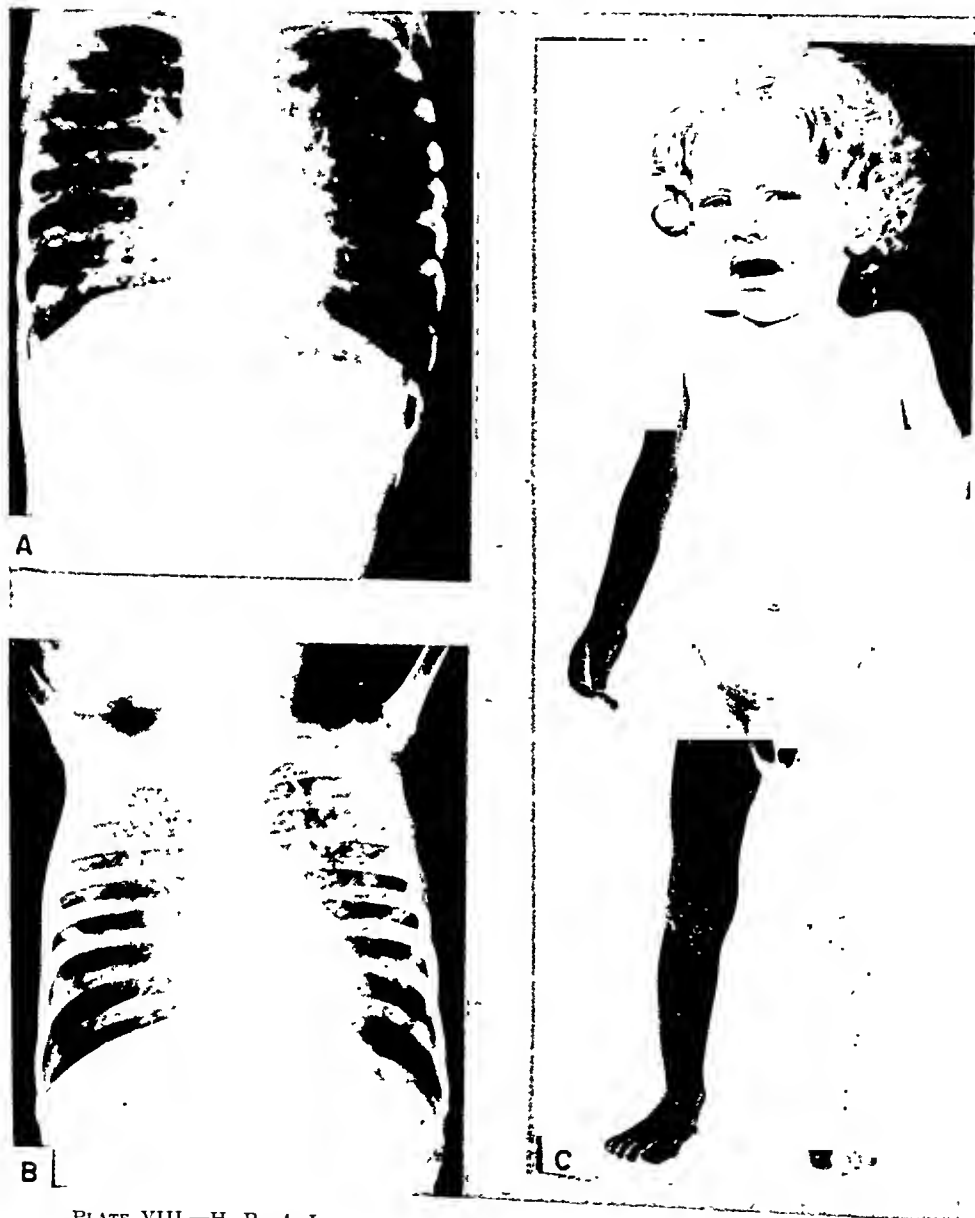


PLATE VIII.—H. P., A, Lungs at 2 years, 10 months.

Emphysema, a natural sequel to partial bronchiolar obstruction may be a serious and eventually even fatal complication of the pulmonary lesion in patients with fibrosis of the pancreas. In certain children this is the most conspicuous feature of the clinical pathology. When it becomes severe, it may cause death from anoxia. Infection is usually not clinically very obvious, but clubbing of the fingers and cyanosis are prominent.

M. T., B, Lungs at 2 years. C, Patient at 1 year, 5 months.

Asphyxia was the most prominent feature of this child's terminal days. The evidence of peribronchiolar infiltration was mild; atelectasis and pneumonitis were minimal but emphysema was extreme. The diaphragm was down to the tenth interspace.





PLATE IX.—E. M., A, Patient at 7 months. B, Heart and lungs at 6 months. C, Patient at 11 months. D, Fingers at 3 years, 7 months. E, Heart and Lungs at 3 years, 6 months. F, Heart and lungs at 3 years 7 months. G, Heart and lungs at 4 years, 3 months. H, EKG at 3 years, 8 months. I, EKG at 3 years, 10 months. J, patient at 4 years.

Heart failure may complicate the disease of patients who have suffered a protracted course characterized not only by repeated and severe pulmonary infection but also severe emphysema.

This child had pneumonitis of a mild degree at 7 months followed by an apparent remission until the age of  $3\frac{1}{2}$  years. However, her chest then showed marked infiltration as well as emphysema. During the next month her heart enlarged considerably and soon thereafter evidence of heart failure was present. At 4 years of age, she had anasarca, cyanosis, marked clubbing of the fingers. An electrocardiogram showed right axis deviation. Terminally, the heart became huge and progressive right axis deviation was demonstrated by electrocardiogram. The abdominal scar is a result of an appendectomy in infancy.

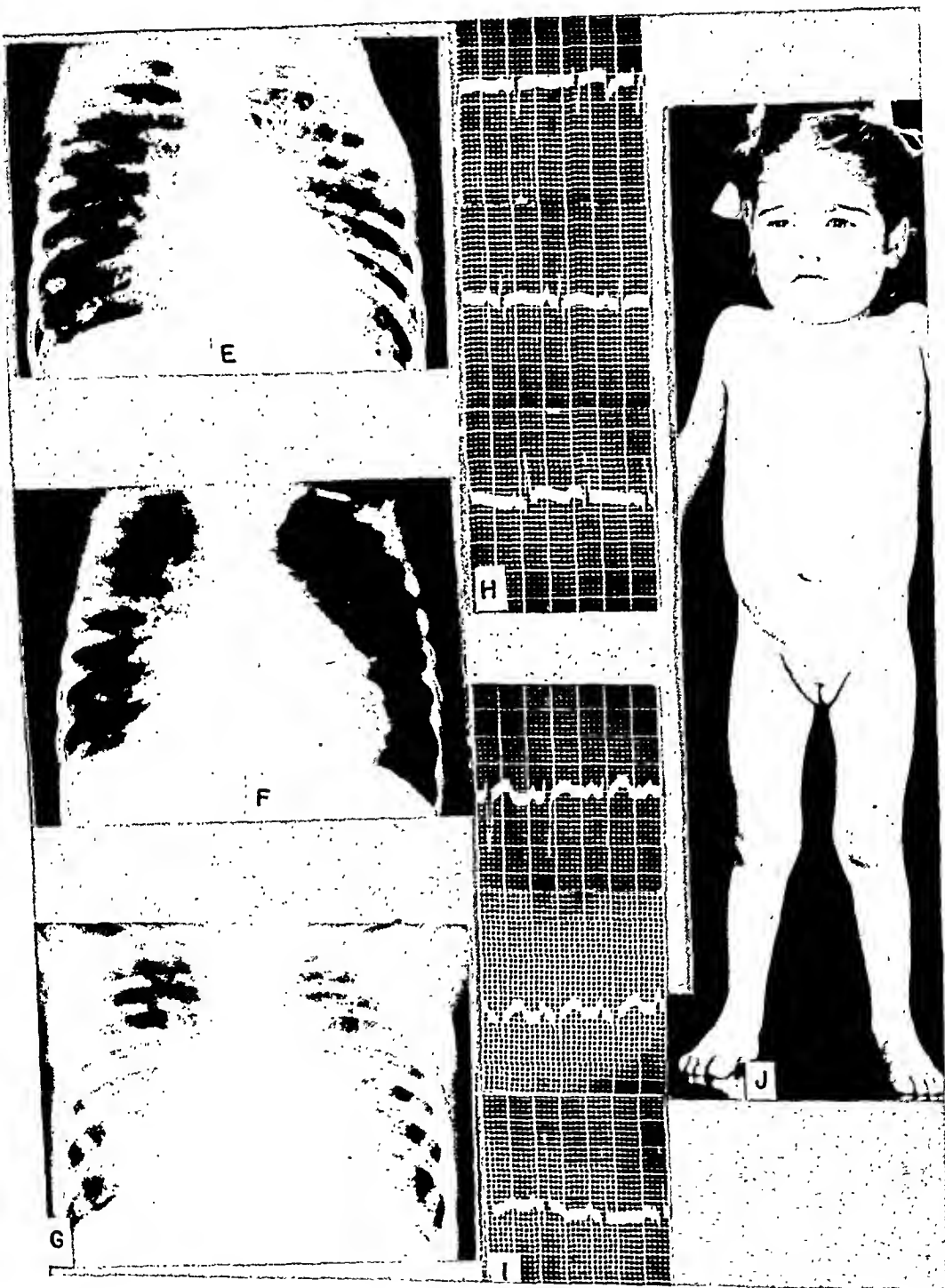


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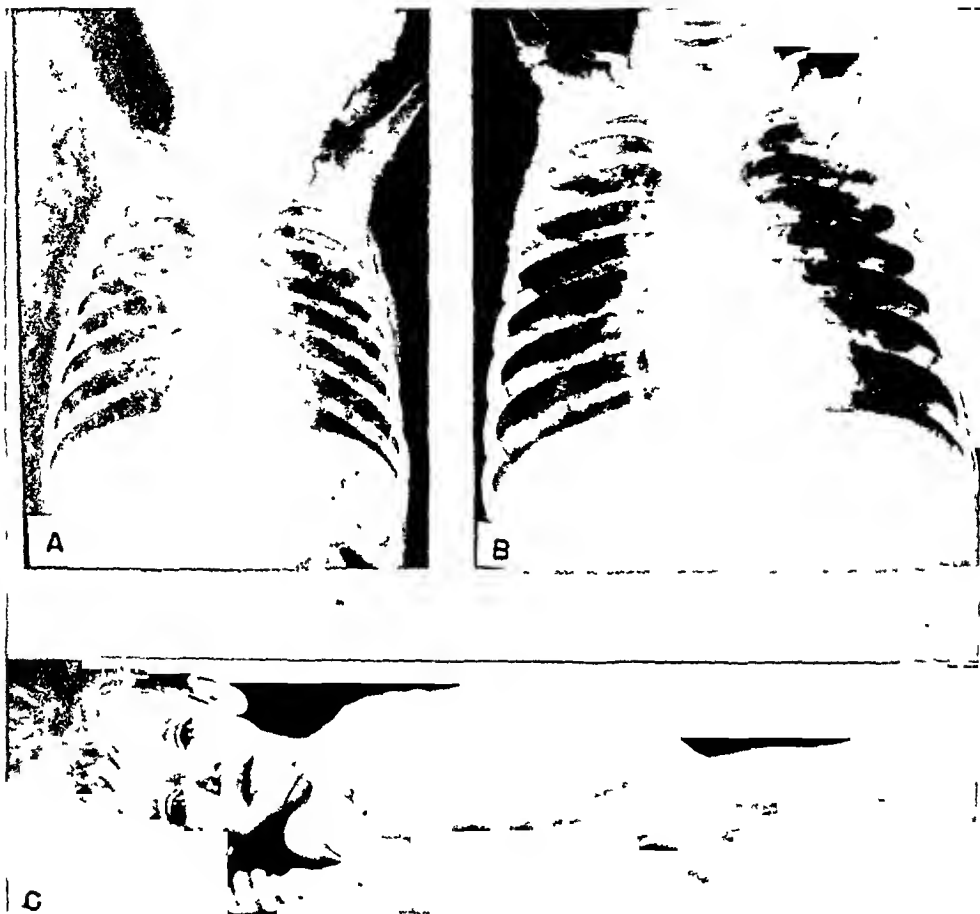


PLATE X—C R. A, Heart and lungs at 7 months B, Heart and lungs at 14 months C, Patient at 12 months D, Heart and lungs at 19 months E, Heart and lungs at 20 months F, Heart and lungs at 20½ months G, Heart and lungs at 21 months

Although all patients who developed heart failure eventually died an occasional patient has had a remission of edema and decrease in heart size for a short period of time

This child was followed closely for eighteen months. A bronchogram made during infancy was not unusual. Progressive dyspnea as well as permanent cyanosis appeared. At 14 months, the heart seemed proportionally larger than it had seven months previously. At 19 months, the heart had increased still further and edema suddenly appeared. Without digitalis but while receiving large doses of the B complex of vitamins her heart decreased in size and the edema disappeared. While receiving the same therapy, her heart suddenly enlarged again and edema returned. From then until the time of death, two weeks later, the edema and heart size both increased. Throughout the period when edema was present, the serum protein was normal.

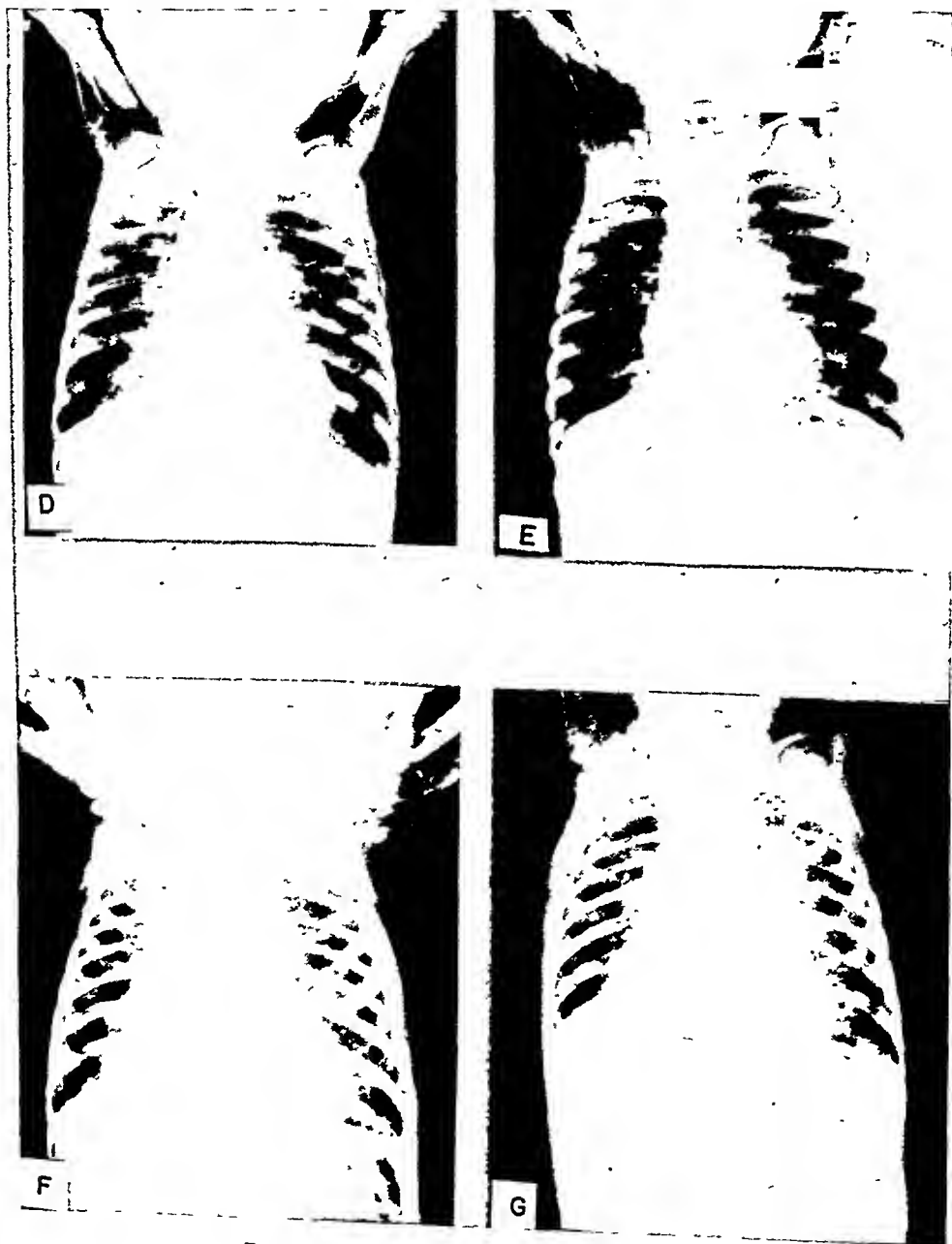


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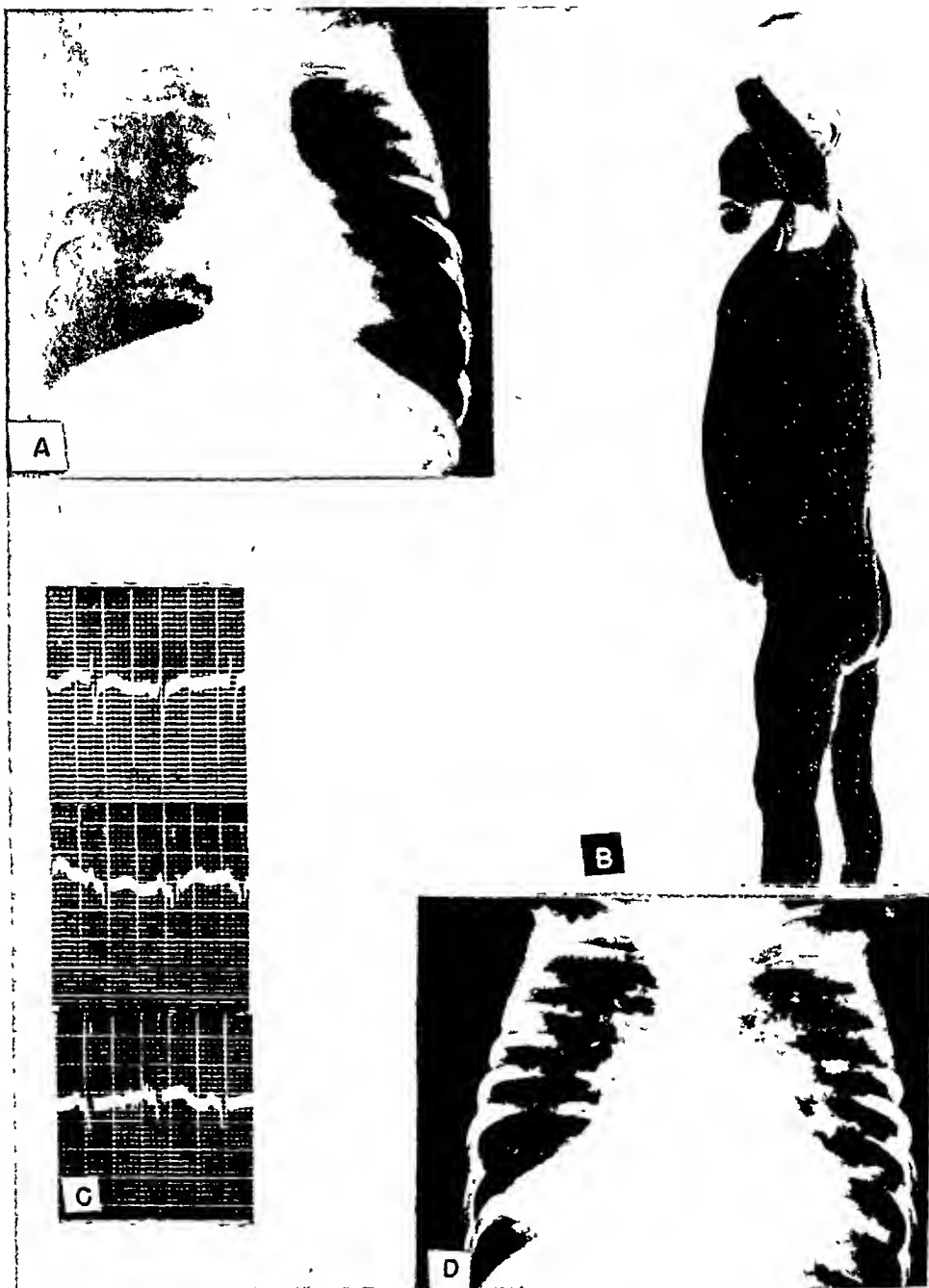


PLATE XI—J. G., A, Heart and lungs at 8 months. B, Patient at 12 months. C, electrocardiogram at 17 months. D, Heart and lungs at 17 months.

The most extreme example of heart failure was encountered in a patient who had severe emphysema and marked infection. Respiratory embarrassment was increased by massive atelectasis. Ascites never developed, and the amount of edema varied considerably during the last three weeks of life. An electrocardiogram showed right axis deviation.



B

PLATE XII—L. P. A, Lungs at 4 months B, Patient at 4 months

Patients surviving meconium ileus for any appreciable time develop pulmonary lesions like other individuals with fibrosis of the pancreas. This child had an ileostomy performed soon after birth, and lived to be 5 months of age, only to succumb to his pulmonary lesion. X-ray of his chest demonstrated emphysema and mild peribronchial infiltration.

scopic finding. Râles, coarse and sticky, are common, frequently persisting in one area for long periods of time. When infection is superimposed the râles are likely to be more numerous and sibilant in character. A striking feature is the discrepancy between the symptoms, which may be flagrant, and the physical findings, which are meager. Often only a roentgenogram reveals the true extent and severity of the pulmonary lesion. The lungs are invariably found to be involved by either physical examination or roentgenogram and almost always in a very widespread fashion.

The roentgenogram proves to be only a more sensitive index of pulmonary changes, particularly emphysema.<sup>27, 28</sup> It is particularly helpful in visualizing the degree of peribronchial infiltration during periods of infection. Viewing

the roentgenogram alone, it is often impossible to construct an accurate picture of the clinical state of the patient or to predict his progress. The clinical and roentgenologic observations together give a clearer conception of the dynamic nature of the process.

The role of infection is most readily discerned by noting the improvement in the clinical course of the patient induced by therapy directed at infection in the lungs. This has been the subject of an extensive report.<sup>26</sup> It seems that only a variable degree of superimposed infection in the lungs adequately accounts for the clinical phenomena. Likewise, it is clear that a basic pulmonary lesion, such as altered secretions, exists, and its progress determines the ultimate clinical course of the patient.

The unique character of the reaction of the lungs to *S. aureus* in the bronchi and bronchioles has already been mentioned. Classical *S. aureus* pneumonia and gross abscess formation rarely occur. Only two of our patients developed *S. aureus* empyema. Even bronchiectasis is surprisingly rare. Only one of the bronchograms done in eight patients with chronic pulmonary lesions revealed bronchiectasis (Plate II).

It appears at times from clinical examination that the element of infection is insignificant. The basic pathology alone appears to produce cyanosis so severe that the patient dies from anoxia. Whether this is due alone to plugged bronchioles, to bronchiolar spasm or to both, remains to be determined. The terminal illness is usually characterized by lethargy, anorexia, normal or subnormal temperature, slight leucocytosis, cyanosis not relieved by oxygen, and a roentgenogram showing severe emphysema. When this type of emphysema is complicated by a more significant degree of infection, the patient becomes feverish and even more desperately ill.

Mention must be made of a dramatic complication we have seen in six patients. After many months of severe dyspnea and cyanosis, accompanied by marked emphysema and widespread lobular atelectasis, the heart became enlarged. The cardiac enlargement may appear in the course of a few days. The enlargement of the heart appears to be due to dilatation at first as it may return equally rapidly to its normal size. But, if the pulmonary situation does not improve, the cardiac difficulty soon returns and hypertrophy develops. Other signs of congestive failure may appear along with the cardiac enlargement. Edema is at times the presenting sign, and ascites has been seen to develop. At first, one might suppose this to be due to a low serum protein concentration resulting from the deficient nutritional state. However, the amazing fact is that most patients have been found to have normal serum proteins and hemoglobin concentrations even when very wasted.<sup>33</sup> The albumin-globulin ratio may be undisturbed. Thus, when edema appears in these patients it is likely to be cardiac in origin. Specific deficiencies of vitamins might be considered either causative or contributory, but large amounts of all the B complex of vitamins given parenterally or orally have had no clear or lasting influence on the course of the cardiac process. Electrocardiograms in various phases of the cardiac complication sometimes show marked right axis deviation, sinus tachycardia, elevation of S-T take-off suggesting myocardial failure, or alteration in the P-R interval. We are inclined to view this cardiac complication as an example of

cor pulmonale. Cor pulmonale appears as a natural consequence of the pulmonary lesion in its severest chronic form and the dynamic concept denies the necessity of singling this group out as a "type." Detailed pathologic and physiologic studies are sorely needed to clarify this interesting and disturbing complication.

A rational therapy of the pulmonary process must be directed at both the thick secretions and the superimposed infection. Aerosol inhalation of antibiotics has been the first substantial advance in the amelioration of the pulmonary process.<sup>25</sup> Again and again the condition of the lungs and the clinical well-being of the patient have been improved when the infection present has been one which yields to such therapy. Clinicians have placed considerably more importance on this response than have the pathologists. We are insistent that, until the basic pathologic process is relieved, the control of the superimposed infection is only ameliorative. Unfortunately, no direct approach to the correction of the abnormal mucous secretion has as yet been devised. We have experimented, in a preliminary way, with the inhalation of substances calculated to liquefy this viscid secretion, with encouraging results. However, close scrutiny of the roentgenograms and physical findings must be demanded whenever a claim is made that the pulmonary lesion has been "cured." Diminution of symptoms and grosser findings are frequently seen in periods of remission but never entirely normal lungs as determined by roentgenogram. We have gradually acquired the clinical impression that the pulmonary process has its inception soon after birth and builds up to a climax of activity some time afterward, usually reaching its most disturbing intensity between 6 and 18 months of age. If this period is survived, the intensity of activity of the pulmonary process seems to subside and those children who have lived 5 to 8 years are often almost free of pulmonary complaints even though once severely affected.

#### THE NUTRITIONAL STATE

The foregoing considerations prepare one to accept the thought that the nutritional state is hardly an independent feature of this disease. The increase in intake of food resulting from increased appetite and adaptation to a lack of pancreatic enzymes may suffice to preserve the nutritional state unless it is undermined by the deleterious effects of infection, loss of appetite, or severe pulmonary disease with cyanosis. Any degree of malnutrition, or a striking preservation of nutrition, may, therefore, be expected, depending on the severity of the basic lesions of the disease. It is inaccurate to consider the tiny scrawny infant as the "type" demanded for fibrosis of the pancreas. All basic manifestations of the pancreatic and pulmonary lesions must be allowed full weight in the diagnosis and in the evaluation of the nutritional state.

There is no convincing evidence that the pulmonary lesion can be prevented or halted in its development by improvement in the nutrition alone. Rather, the nutritional state may depend to a great extent on the pathologic changes in the lungs. If the pulmonary lesion has never been conspicuous, the nutritional state and growth may not be appreciably disturbed, even if the signs of pancreatic insufficiency have been present since birth. No one can deny that it would be better to face infection in a well-nourished condition. But, no unique



or specific causal relationship between the nutritional state and the basic pulmonary lesion has been demonstrated. It is imperative to recall the other factors that we have mentioned which by their balance determine the nutritional state.

Above all, the physician should be wary of subtracting items of food from the diet on the basis of "suspected" intolerance. One is more likely to interfere with the natural compensation of increased intake by withdrawing food for which the patient is eager. Attention had better be directed to the provision of a complete, well-balanced diet in amounts calculated to satisfy the appetite.<sup>26</sup> One should not become guilty of treating the stools rather than the child.

#### CONCLUDING COMMENTS

Sympathy is felt with those who weary of exhaustive descriptions of this disease. Yet such delineations must serve to get the stage set for the more exciting event, discovery of the actual cause. Limited attempts to reproduce the disease in animals have brought but equivocal results.<sup>30</sup> The common hypotheses regarding etiology which relate it to infection, nutritional deficiency, disturbed function of the autonomic nervous system, or allergy, have not as yet enabled anyone to pry out the secrets of pathogenesis. It is clear that the disease is hereditary in origin, being a Mendelian recessive characteristic.<sup>31-33</sup> Baggenstoss<sup>34</sup> has added an intriguing concept of pathogenesis, that of congenital inability of the affected individuals to produce secretin in the duodenum, with resultant inspissation of pancreatic secretion.

The validity of any classification of the disease into distinct "groups" or "types" is challenged. Selection of abstract types will only leave the bulk of patients in a "mixed" group and lure the untutored clinician into a succession of surprises as he faces natural developments. The clinical manifestations are the natural consequence of the close relation between the systems affected and the dynamic features of the disorder.

We are grateful to Dr. E. D. B. Neuhauser for his permission to reproduce the x-rays and for his guidance in their interpretation. We are deeply aware of the efforts of many of the staff of the Children's Hospital, Boston, who made the accumulation of these data possible.

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## INJURIES IN CHILDHOOD

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**E**XACTLY how many children are disabled because of accidents has never been accurately determined. In Pennsylvania approximately 900 children lose their lives each year as the result of accidents. Nearly 12,000 children between the ages of one and 14 years die annually of accidents in the United States.

This past fall a campaign to reduce child accidents has been developed under the sponsorship of the Metropolitan Life Insurance Company in cooperation with the U. S. Children's Bureau, the American Academy of Pediatrics, and the National Safety Council. The Pennsylvania Department of Health has actively participated in this campaign.

Certain facts have been emphasized in this campaign, among which the following merit citation:

1. Accidents are the leading cause of death and an outstanding cause of permanent and disabling injuries among children more than one year of age.
2. In the past thirty five years, the death rate from disease among children one to 14 years of age has been reduced more than 80 per cent. On the other hand, the reduction in the death rate from accidents has lagged behind.
3. After infancy, more children die as the result of accidents than from any single disease. In the ages from one to 14, inclusive, accidents take as many lives as pneumonia, diarrhea and enteritis, measles, diphtheria, meningitis, poliomylitis, whooping cough, and scarlet fever combined.
4. Forty per cent of all accidents among children from one to 14 years of age occur in the home.
5. Burns are the cause of most fatal home accidents.
6. Falls head the list of serious nonfatal accidents.
7. Safety in the streets is extremely important, as indicated by the number of child injuries sustained through vehicle accidents. It has been estimated that more than one third (34 per cent) of all fatal accidents result from motor vehicles.
8. A more critical attitude toward the cause of accidents is being developed by physicians and others interested in this field. There is more to injuries, especially when of a repeated nature, than "bad luck" or evil spirits. In the same way that some adults are more susceptible to accidents than others, so certain children seem to have emotional and psychic factors which predispose them to injury. In Rochester, N. Y., a clinic has been sponsored by the Medical School and the City Health Bureau to study this problem of accident prone children and their families. Children who have been seen on more than one occasion in the accident dispensary are being studied from a physical and psychological standpoint. Their home environment is investigated. There is a close relationship between safety and good health—not only physical health, but emotional health as well. There is evidence to show that a child who is unhappy or who lacks self confidence may express his unhappiness, often without being aware of it, in the form of hurts and injuries to himself. The youngster who is receiving more than his share of mishaps should be scrutinized from this point of view.

9. When considering the problem of injuries in childhood, the child's personality, his muscular coordination, his physical environment, and the parents' emotional attitude toward the child are factors which merit close study.
10. Two factors characteristic of child development are frequently at the root of accidents—the desire of children to imitate others, especially their parents, and their fondness for repetition. If parents are heedless, the child may follow suit. If a child performs a hazardous act and avoids disaster, he is likely to repeat the procedure. His curiosity is liable to lead to his destruction.
11. Personality maladjustments in childhood, impaired vision or hearing, all may play a role in the accidents of childhood, particularly when repeated accidents occur.
12. The problem of child safety is one for the family and the entire community. It is rightfully a phase of public health education because accidents affect the well-being of a community. It is a subject of importance not only to the family, but to child study groups, which emphasize child hygiene, as well. Among other groups who are concerned with this problem are social agencies, city departments of health, education, police, fire prevention and housing authorities, chambers of commerce, automobile clubs, and, of course, safety councils.
13. The two outstanding causes of accidents are: unsafe conditions and unsafe practices.

With this general outline of the nature and scope of the problem we wish to consider the problem of childhood injuries from a local standpoint.

For the purpose of this study we have reviewed the records of all children 18 years of age and under who were seen at St. Luke's Hospital from June 1, 1948, to Aug. 31, 1948, inclusive. This study pertains only to those children who, following an accident, were seen at the hospital dispensary, and does not include those examined and treated by family physicians, other hospitals, or who perhaps did not require medical attention.

In this period of three months, 566 children were seen at St. Luke's Hospital for injuries sustained as the result of an accident. Four hundred two (71 per cent) were males; and 164 (29 per cent) were females. We have analyzed and investigated this group in various ways: the mechanism of the injury, the scene of the accident, the time of day the injury was sustained, and the nature of the injury have been reviewed and tabulated. We have analyzed this group with respect to the number requiring hospitalization, the number receiving antibiotics and prophylactic tetanus antitoxin or toxoid, the types of treatment that were employed, and the number requiring x-ray studies and anesthetics. Further, we have broken down several of the groups for more detailed analysis. While the time period covered in this analysis is brief (three months) the number of children involved makes the study of statistical value.

We have found that about six children a day were seen in the hospital dispensary because of an injury, and that over six children were admitted each week to the hospital for more complete therapy or study. (Table I.)

TABLE I.

Number of children	566			
18 years of age and under		Male	402	(71%)
		Female	164	
Number admitted to the hospital			83	(14.6%)
Number of hospital days			646	(1 to 70)

In analyzing our patients with respect to age, it was found that more children between the age of 2 and 3 years were injured than at any other age period. The next largest group was that between the age of 5 and 6 years. (Fig. 1.)

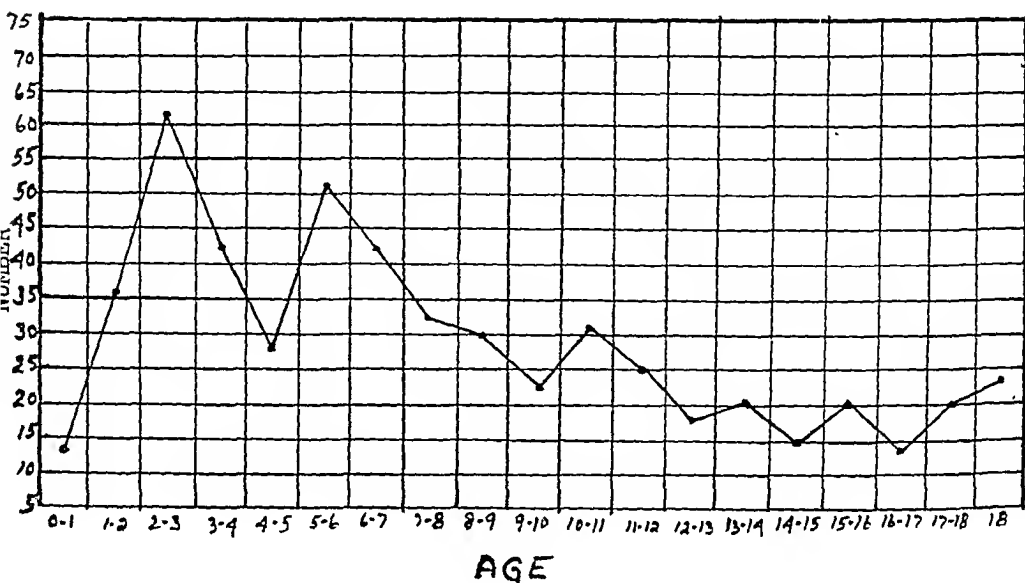
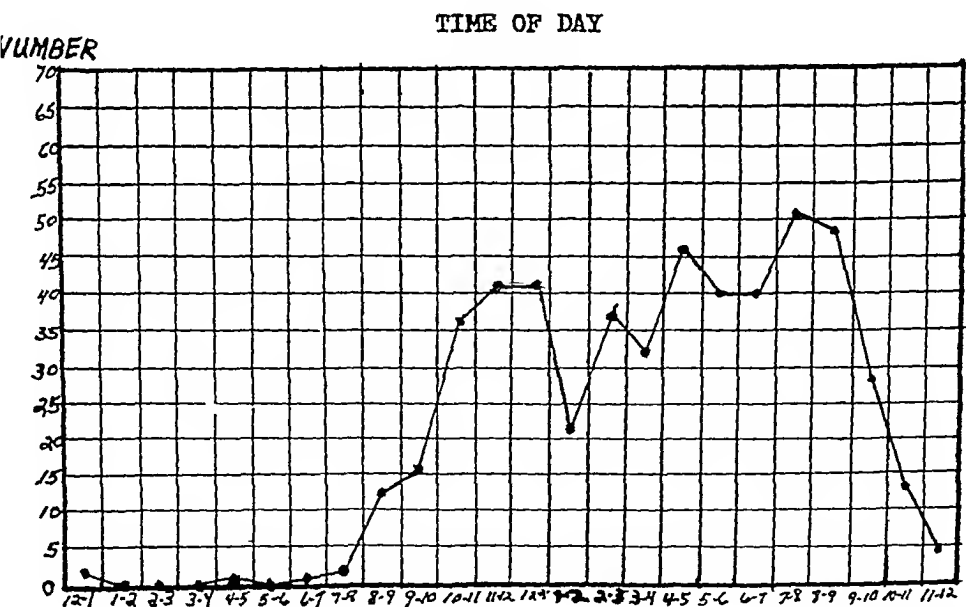


Fig. 1.



Not stated: 41

Fig. 2.

The fact that the majority of injuries in childhood occur after the noon hour is shown graphically in Fig. 2. Over 78 per cent of all accidents happen after 12 noon with the peak being between 7 and 8 P.M. However, a survey in the winter months might show the greatest number of accidents occurring at an earlier hour.

The scene of the injury is indicated in Table II. About three out of every four injuries were sustained either in or about the home or on a city street. The fact that this study was undertaken during the summer months would indicate that the number of injuries sustained in the school might be lower than a similar survey taken during the school year. The number of accidents that occurred in the hospital is explained by the use of the hospital dispensary for minor first aid to hospital employees or student nurses. Only seven accidents occurred on a farm in this series. Perhaps the country practitioner is able to treat most of these cases in his office, rather than finding it necessary to refer them to the hospital.

TABLE II. SCENE OF INJURY

Home	316	Garage	1
City street	106	Bank building	1
Playground	42	Store	1
Not stated	16	Church	1
School	16	Social hall	1
Hospital	10	Camp	2
Swimming pool	10	Woods	1
Factory	8	River	1
Farm or field	14	Bridge	1
Baseball field	4	Police station	1
Canal	3	Seashore	1
Reservoir	2	Day nursery	1
Automobile	2	Creek	1
Country club	2	College campus	1
		Total:	566

Falls accounted for almost one out of every three injuries sustained by these children. (Table III.) Considering the large number of children taking part in sports during the summer months, the number sustaining sports' injuries is not high, being only 6 per cent of the entire group. When automobile, motorscooter, and bicycle injuries are totaled, it is noted that about one child in ten becomes injured as the result of a vehicle accident. Perhaps this number would also be higher if a similar study were undertaken during the winter months when school attendance places the largest number of children on the streets at one time. A review of the miscellaneous injuries indicates that almost anything that can happen to a child usually does. He has not yet learned through experience.

Almost one-half of these children (259, or 46 per cent) were given either toxoid or antitoxin to prevent tetanus. While the value of this is questioned by some, it is considered by the surgical services of the hospital an important step in treatment. In all but the most minor injuries, tetanus prophylaxis is routinely performed, being preceded by a skin sensitivity test. In recent years

TABLE III. MECHANISM OF INJURY

<i>Falls:</i>	32.8%	<i>Playground injuries</i>	19
"Fell"	51	Swing, sec-saw, sliding board, sandbox, etc.	
Fell from height	23	<i>Puncture wounds</i>	18
Fell on concrete, cement, sidewalk, curb, etc.	25	Sticks, pencil, pen, etc.	
Fell down steps	18	<i>Gun injuries</i>	5
Fell on glass	21	<i>Foreign body in eye</i>	9
Fell out of bed	8	<i>Stepped or fell on nail</i>	18
Fell out of chair	4	<i>Stepped on sharp objects</i>	8
Miscellaneous	36	<i>Splinter injuries</i>	2
<i>Animal bite:</i>	46 (8%)	<i>Hit by stone</i>	11
a. Dog	45	<i>Struck by door</i>	6
b. Cat	1	<i>Insect bites</i>	6
<i>Sport injuries:</i>	33 (6%)	<i>Toy injuries</i>	3
Baseball	19	<i>Ingestion of foreign body</i>	13
Other	14	Pin	4
<i>Winger injuries</i>	12 (2%)	Stone	1
<i>Automobile injuries</i>	29 (5%)	Button	1
Struck by auto	15	Iodine	1
Bumped into car	6	Turpentine	1
Fell off car	6	Ant poison	1
<i>Motor scooter</i>	5 (0.9%)	Rubbing alcohol	1
<i>Bicycle</i>	26 (3.7%)	Metal toy	1
<i>Carriage injuries</i>	5	Stick	1
<i>Burns</i>	21	Dress snap	1
Electric household appliances	8	<i>Farm accidents</i>	5
Firecracker	3	<i>Pulled up suddenly by hand</i>	3
Hot fluids	3	<i>Tool or machine injuries</i>	5
Flammable liquids	2	<i>Knife or scissor injuries</i>	3
Other	5	<i>Not stated</i>	17
<i>Swimming accidents</i>	15	<i>Miscellaneous</i>	37
		<b>Total:</b>	<b>566</b>

no case of tetanus has been seen at the hospital in which this step had been neglected. Similarly, the use of antibiotics prophylactically is being carried out. Fifty-six of the ninety children who received penicillin were given one dose, this being 300,000 units of water-soluble crysticillin.

One out of every five children seen in this group required the use of an anesthetic, and it is interesting to note that of this number almost three out of every five received local anesthesia. A number of the fracture cases were treated by an infiltration of the fracture hematoma with procaine, and even lacerations in the older children were at times repaired under local anesthesia.

TABLE IV. ANESTHETICS

<i>General anesthesia:</i>		
Nitrous oxide	8	
Ether	39	
Pentothal	1	Total: 48
<i>Local anesthesia:</i>		
Novocaine	65	
Ether chloride	2	Total: 67
Total number of children receiving anesthetic	115	(20%)

One out of every three children (183 in all) examined this past summer at the hospital for injuries had radiographs and in eighty-two instances, there were positive findings. The large number of negative findings might be reduced if all children were examined by more experienced surgical residents. The facili-

ties of the x-ray department are open constantly, and radiographs are employed almost entirely to the exclusion of fluoroscopic examinations.

The large number of fractures of the upper extremity seen in this study is noteworthy. Fractures of the radius and ulna, either alone or together, constituted the greatest single group of fractures seen in children, amounting to twenty-nine of a total of seventy-one with fractures.

A grouping of the diagnoses is presented in Table V.

TABLE V. DIAGNOSES

Lacerations	205
Contusions	53
Puncture wounds	60
Abrasions	38
Fractures and dislocations	79
Sprains	23
Foreign bodies	24
Concussion of brain	19
Burns	21
Negative	11
Cellulitis	11
Subluxation of joint	2
Lacerated tendons	4
Not stated	9
Avulsion of fingernail	4
Miscellaneous	3
Total:	566

The repair of lacerations by sutures was carried out in 125 cases (Table VI). Although the total number of treatments is only 370 for this group, it is assumed that various other therapeutic measures may have been performed and not noted on the hospital dispensary records. Eleven major surgical procedures were required in this group. [Laparotomy, craniotomy, arthrotomy, excision of loose bone from the elbow region, amputation of finger, open reductions of fractures (two), and suturing of lacerated tendons (four).]

TABLE VI. TREATMENTS

Sutures	125	Open reduction of fracture	2
Skin clips	1	Stomach lavage	2
Ointment and dressing	33	Decompression of nail bed	2
Dressing	52	Strapping	15
Cast	32	Reduction of dislocation	1
Reduction of fracture and cast	18	Arthrotomy of knee	1
Splints	17	Laparotomy	1
Removal of foreign body	14	Craniotomy	1
Cauterization	18	Traction	1
Débridement of burns	8	Excision of loose bone	1
Incision and drainage of abscess	6	Amputation of fingertip	1
Cleansing of wound	6		
Suturing of lacerated tendon	4		
Sling	6		
Reduction of nose fracture	2	Total:	370

## CHILDREN UNDER ONE YEAR OF AGE

The types of injuries sustained in children under one year of age are variable. In this group (Table VII), there were three instances in which no injury had been sustained. The number of burns sustained by infants points toward carelessness on the part of the mother.



TABLE VII. ANALYSIS OF CHILDREN UNDER ONE YEAR OF AGE

Number	14		
Age	From 2½ to 10 months (Average: 6 months)		
Scene of injury	Home in all cases		
Diagnosis:			
No injury	3	Concussion of brain	1
Burns	3	Foreign body in eye	1
Puncture wounds	2	Contusion	1
Lacerations	2	Subluxation of joint	1
Mechanism of injury:			
Fell out of crib	3		
Fell from high chair	1		
Bitten by cat	1		
Pulled up suddenly by hand	1		
Carriage rolled down steps	2		
Coffee spilled over feet	1		
Hot water spilled on hand	1		
Head bumped rusty nail	1		
Leg was wrenched	1		
Electric hot plate burn	1		

An analysis of the wringer injuries (Table VIII) is of interest in that ten of these twelve children had x-rays and in every instance the radiograph was negative for bone injury. In only one case was there a laceration, all other children sustaining contusions. As would be anticipated, the average age of this group indicates that the preschool child is the one most likely to sustain a wringer injury.

TABLE VIII. WRINGER INJURIES

Number of cases	12
Average age	4 years (2-10)
Time of day	10:30 A.M. average time for group
X-rays	10 patients (all negative)

It was interesting to note that the average time of injury for the children sustaining dog bites was 4:00 P.M., and only five occurred before the noon hour. The types of injuries sustained are indicated in Table IX. For the most part,

TABLE IX. ANALYSIS OF DOG BITE GROUP

Number of patients	45
Age	7.4 years (average)
Time of day	4 P.M. (average time: only 5 before noon)
Scene of injury:	
Home	17
Street	19
Neighbor's home	3
Miscellaneous	4
Not stated	2
Diagnosis:	
Puncture wounds	17
Lacerations	17
Abrasions	10
Contusions	1
Part of body involved:	
Scalp and face	14
Trunk	5
Upper extremity	10
Lower extremity	16

a review of these records indicates that none of the puncture wounds, lacerations, or abrasions were of significance, although cauterization was carried out in eighteen cases.

The value of the State legislation prohibiting the use and sale of firecrackers is demonstrated in Table X. Only three children this past summer were seen at the hospital for injuries sustained as the result of playing with firecrackers. While we have no statistics to indicate what percentage reduction this is as compared to fifteen years ago, it would appear that this type of injury has become a negligible one. The burns that were sustained in the hospital, four in number, occurred either among kitchen employees under the age of eighteen years burned by heating units or by student nurses in the training school laboratory.

TABLE X. ANALYSIS OF BURNS

Number	21
Average age	8.8 years (3 under 1 year)
Average time of day	3:45 P.M.
Scene of injury:	
Home	15
Hospital	4
Factory	1
Seashore	1
Types of burns:	
Electric household appliances	8
Firecrackers	3
Hot fluids	3
Sunburn	2
Flammable fluids	2
Acid	2
Not stated	1
Total:	21

It is apparent from the analysis of the automobile injuries that boys are involved more often than girls and this group constitutes the number with the most serious injuries, there being nine fractures and three concussions reported. The mechanism of the injury and the scene of the injury are itemized in Table XI.

TABLE XI. ANALYSIS OF AUTOMOBILE INJURIES

Number	27
Average age	7.5 years
Time of day (average)	4 P.M.
Scene of injury:	
City street	18
Home	3
Road	2
In auto	2
Picnic grove	1
Not stated	1
Mechanism of injury:	
Struck by	15
Fell from	6
Bumped into	6

Bicycle and motorscooter injuries, thirty-one in number, are analyzed in Table XII. The age group here is higher than in the automobile injuries, being 9.3 years for the group.

TABLE XII. BICYCLE AND MOTORSCOOTER INJURIES

Number	31
Average age	9.3 years
Time of day	5 P.M. (only 3 before noon)
Mechanism of injury:	
Fell from	21
Pedal injury	5
Struck by car	3
Scared by car	1
Not stated	1
Scene of injury:	
City street	18
Home	10
Playground	2
Not stated	1

Of all of these children 13.3 per cent sustained fractures. Such injuries were twice as common in boys as in girls, and of the seventy-five children with fractures who were analyzed, twenty-six were admitted to the hospital; thirty-three required an anesthetic. The average time of day before and after the noon hour is indicated in Table XIII, and the mechanism and scene of injury are likewise analyzed here.

TABLE XIII. ANALYSIS OF FRACTURES

Number	75
Average age	8.8 years
Time of Day:	
Before noon	15 (Average time: 10:15 A.M.)
After noon	57 (Average time: 6:15 P.M.)
Not stated	3
Mechanism of injury:	
Fell from height	19
"Fall"	12
Sport injury	14
Auto injury	9
Bicycle injury	7
Fell from horse	2
Hit by fist	2
Miscellaneous	10
Scene of injury:	
Home	29
Street	20
Playground	15
School	4
Farm	3
Factory	1
Miscellaneous	3
Total:	75

## SUMMARY AND CONCLUSIONS

1. That 566 injured children were examined and treated in the accident room of St. Luke's Hospital in Bethlehem in a three-month period indicates that the problem of child safety is one of sufficient magnitude to warrant continued and more detailed study.

2. Of the accidents last summer, 55.8 per cent occurred in the home and 18.7 per cent on one of the city streets.

3. It was necessary to admit 14.8 per cent of the patients to the hospital for further treatment or study.

4. There were no deaths from injuries in the group of children reviewed for this study.

5. More injuries occurred in children between 2 and 3 years of age than at any other age. The next largest group was that between 5 and 6 years. 62 per cent of all children analyzed in this study were 9 years of age or under.

6. Seventy-eight per cent of all injuries occurred after noon, with the largest number of accidents occurring between 7 and 8 P.M.

7. Concerning the mechanism of injury in this series, it has been demonstrated that injuries result from:

Falls	32.8 per cent
Animal bites	8 per cent
Sport injuries	6 per cent
Automobile injuries	5 per cent
Bicycle injuries	4.6 per cent
Burns	3.7 per cent

8. Twenty per cent required an anesthetic and in those instances in which one was employed, in 58 per cent of the cases local anesthesia was administered.

9. Thirty-three per cent required x-ray study.

10. In 64 per cent of the cases, lacerations, contusions, abrasions, and puncture wounds were the primary diagnoses. In 13.3 per cent the diagnosis was a fracture of a bone.

11. It is virtually impossible to analyze a group of this type from the standpoint of end results. However, a careful examination of the hospital records would indicate that the vast majority of these injuries were not of a serious nature. It would be our impression that injuries are not a major cause of crippling from a percentage standpoint. We are unable, however, to support this feeling statistically at this time.

12. Two thoughts are developed from this study:

(a) The large number of children who go directly to the hospital dispensary for treatment apparently by-passing the family physician; (b) The service which the hospital unfailingly renders to the community in being prepared day or night to accept these injured children for any type of therapy no matter how slight or drastic, and to have available twenty-four hours a day all facilities so necessary to prompt and efficient treatment. Physicians, nurses, technicians, and orderlies are always on call with adequate reserves. The use of the operating room, the x-ray department, the blood bank; the availability of antibiotics, tetanus prophylaxis, opiates, stimulants, and special instruments, is a source of wonder even to those who work day in and day out in this environment.

13. Finally, figures are impersonal, and do not disclose the personal and family tragedies covered by these numbers which seem to rise higher year by year. One writer states that, "we have conquered pestilence and are eliminating the life-destroying infectious diseases of the past, but we permit the automobile, the modern plague which has turned our highways into roads of disaster and

death, to erase our victories." Our record of injuries, even in childhood, is a terrible record, and it becomes all the more depressing when we remember the estimate of the Traveler's Insurance Company that 98 per cent of all accidents can be prevented.

We would submit for consideration that a special committee to study this problem locally, headed by a pediatrician, might be of immense value to the community.

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## SEROTHERAPY IN PERTUSSIS

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THOUGH a preventable disease, whooping cough still affects large numbers of infants and children in many sections of this country where the practice of preventive medicine has not kept pace with scientific progress. The disease is well known to be of grave import in the infant under 6 months of age in whom immunization has not generally been practiced, because of the prevailing opinion that the mechanisms for producing active immunity in this age group are immature.<sup>1</sup> The validity of this opinion is to be doubted, however, in the light of recent studies relative to pertussis immunization in early infancy.<sup>2, 3, 4</sup>

The challenge of a common disease in infancy associated with high mortality and with immediate as well as late pulmonary and possibly central nervous system complications has resulted in many studies related to specific therapeutic agents against active pertussis during the past ten years. Despite great advance in antibiotic therapy which has been shown to be very effective against the frequent and serious bacterial complications of this disease, the primary agent has not yet been conquered. Suggestive experimental studies with streptomycin have been made<sup>5, 6</sup> and clinical evaluation with this agent is in progress but not yet reported. Many studies relating to the effectiveness against whooping cough of specific antiserum of both human and animal origin have been published in the past ten years with uniformly favorable conclusions where hyperimmune human serum was used but with far less enthusiasm for the efficacy of rabbit serum.

The present study was undertaken with the view of comparing the effectiveness of three types of antisera with each other, as well as with concomitant controls. The diagnosis of whooping cough was based primarily on clinical grounds and substantiated in the great majority of instances by the characteristic lymphocytic response, or by positive nasopharyngeal cultures in the few questionable cases.

The plan of study was essentially to treat patients with cases of similar severity and duration in the same age groups with the three types of therapeutic sera, and to secure a more or less simultaneous group of similar untreated controls. It was impossible to alternate cases for treatment and control because of the marked variation in severity, age, and duration of disease on admission, and because of the variability of the supply of the various sera. Nevertheless, it is felt that with detailed histories and careful observation of

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the patients' course and condition during the first two to five days of hospitalization, together with pertinent laboratory and x-ray studies, we were enabled to place the cases in rather definite categories, so that within a given period of one to two weeks at least one or more patients of similar age, severity, and duration of disease could be placed in each of the four divisions of the study.

With a view to evaluation of results certain procedures were followed in all cases, and included all criteria used in previously published reports so that some common denominator might be at hand whereby comparisons might reasonably be made. Thus, severity of illness on admission was determined by the history, duration, frequency and severity of paroxysms, the state of nutrition, frequency of vomiting, episodes of cyanosis, and degree of pulmonary involvement. In almost every case a period of two to five days elapsed after admission during which there was ample opportunity to gauge the overall picture of the illness, particularly with reference to the severity and frequency of paroxysms, whoops, periods of cyanosis, and vomiting. All of these were rather accurately charted by the nursing staff, which was instructed concerning the importance of these observations and the charting throughout the patients' entire hospitalization. They had no preconceived notions as to the efficacy of any of the sera being used. Throughout the period of study at least one of us was in fairly constant attendance on the wards, and we feel that though a goodly number of paroxysms were unobserved or uncharted, especially at night when the nursing staff was cut down, nevertheless, a great majority of these were recorded and constituted what is probably the single most objective clinical estimate of the severity and progress of the illness.

Additional observations which appeared pertinent to the study included patients' weights on admission and twice weekly thereafter, chest roentgenograms on entry and at weekly intervals during hospitalization, frequent agglutination studies on most of the treated patients and on several of the controls, and finally hemoglobin estimations together with white cell and differential counts on all patients at the time of admission and once weekly thereafter.

This series comprises a total of 150 consecutive cases of pertussis admitted from October, 1946, through December, 1947. Of these, forty-eight were untreated controls, thirty-eight received a refined horse hyperimmune serum,\* thirty-three received a refined, concentrated, globulin fraction obtained from the serum of rabbits which had been immunized repeatedly with killed cultures of Phase I *Hemophilus pertussis* as well as a pertussis endotoxoid,† and thirty-one received a concentrated globulin fraction prepared from human hyperimmune serum.‡ All treated patients in the series were in the paroxysmal stage of the disease.

Table I indicates age distribution and type of serum employed in the various patient divisions.

\*Supplied by Lederle Laboratories.

†Supplied by Ayerst, McKenna, and Harrison Ltd., Montreal, Canada

‡Supplied by Cutter Laboratories, Berkeley, Calif.

TABLE I. ADMISSIONS FOR WHOOPING COUGH, OCTOBER, 1946, TO DECEMBER, 1947, WITH AGE DISTRIBUTION AND TYPE OF SERUM THERAPY

AGE	TOTAL ADMISSIONS	HUMAN SERUM	RABBIT SERUM	HORSE SERUM	CONTROL
0-6 months	31	9	6	6	10
7-12 months	37	8	9	12	8
1-8 years	82	14	18	20	30
Total	150	31	33	38	48

## DOSAGE

*Horse Antipertussis Serum.*—At the beginning of the study single doses of 10,000 to 20,000 units intramuscularly were used, the smaller doses for the younger infants. When these appeared to be ineffective the dose was increased to as high as 75,000 units, the average dose for all patients being 40,000 units. The usual precautions taken in all foreign serum therapy were carried out, and the only reactions which appeared were two instances of transient urticaria. The great majority of patients received the entire amount in one injection, the remainder receiving no more than two injections on consecutive or alternate days.

*Rabbit Antipertussis Serum.*—At the outset single doses of 10,000 units intramuscularly were employed. Ineffectiveness of this dose seemed apparent early in the study, and subsequent doses were scaled to as high as 75,000 units in the more severe and older patients, the combined average among all patients being 40,000 units. Again practically all patients received the entire dose in one injection, the remainder receiving no more than two doses at one- or two-day intervals. No untoward reactions to this serum were noted.

*Human Hyperimmune Antipertussis Serum.*—Of this 2.5 c.e. are equivalent to 20 c.e. of the original serum. The dosage varied from 2.5 c.e. (two cases) to 10 c.e. (ten cases), with an average of 7.5 c.e. Twelve patients received two injections on successive days, the remainder received the entire amount in one dose. There were no local or systemic reactions to this serum.

## RESULTS

Following are figures representing summary of course of the disease. Figures are averages obtained from individual charts.\*

	CASES TREATED IN FIRST WEEK			CASES TREATED IN SECOND WEEK			CASES TREATED IN THIRD WEEK		
	A	B	C	A	B	C	A	B	C
Controls	7	24	22	7	28	21	5	27	15
Horse serum	6	25	18	6	29	19	5	44	27
Human serum	6	26	22	3	28	17	4	39	33
Rabbit serum	11	33	29	5	30	20	8	51	37

\*A, days after treatment that the peak of the disease was reached (or the days after entry in the controls).

B, the total duration of the paroxysms in days.

C, the duration after treatment (or after entry in the controls), in days.

Examination of the above figures fails to reveal any marked difference in the clinical course of the four groups of patients. A breakdown of the cases



according to the dosage of serum used fails to show any difference in those patients treated with larger doses or with multiple doses.

Table II shows the distribution according to severity, with subsequent courses judged on the basis of definite improvement, no improvement, or worsening of condition. Improvement was based on decided decrease in coughing and vomiting within three to four days after serum therapy, and on improvement in appetite and general appearance of the patient.

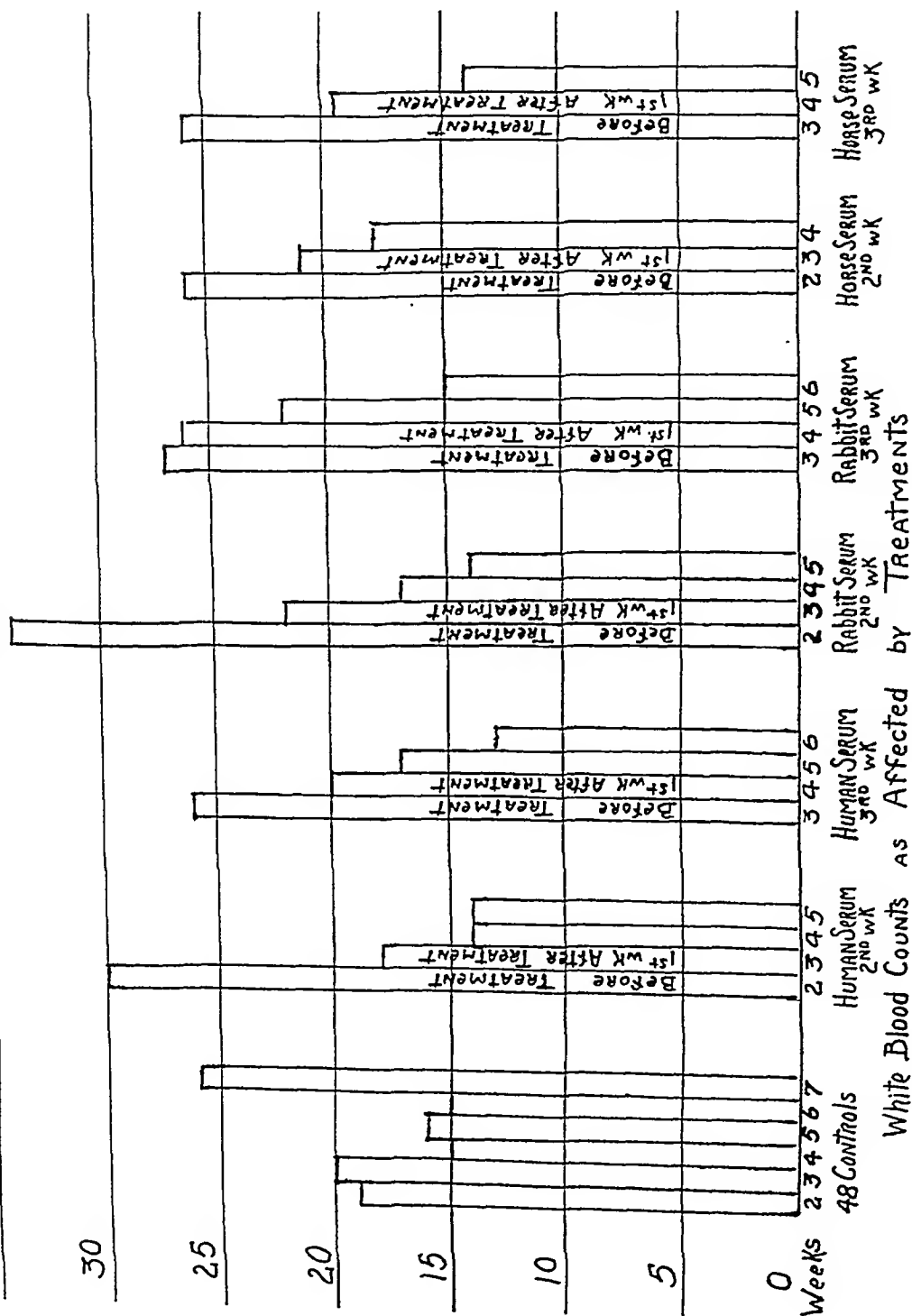
TABLE II. DATA ON SEVERITY ON ADMISSION, WITH RESULTS OF SERUM THERAPY

AGE	SEVERITY OF DISEASES ON ADMISSION			SUBSEQUENT CONDITION		
	MILD	MODERATE	SEVERE	IMPROVED	UNCHANGED	WORSE
Human Serum						
0-6 months	2	5	2	—	9	—
7-12 months	1	7	—	1	7	—
1-8 years	4	7	3	—	12	2
Rabbit Serum						
0-6 months	2	4	—	—	5	1
7-12 months	3	5	1	—	9	—
1-8 years	3	10	5	3	14	1
Horse Serum						
0-6 months	1	5	—	1	3	2
7-12 months	4	7	1	1	10	1
1-8 years	4	7	9	1	17	2
Controls						
0-6 months	5	4	1	1	6	3
7-12 months	4	3	1	—	7	1
1-8 years	15	12	3	4	22	4

A breakdown of the above cases according to the week of disease in which serum treatment was given does not indicate any significant differences in response of patients treated early or late.

Some of the previously reported series treated with human hyperimmune serum have emphasized the occurrence of a significant decrease in lymphocytosis shortly following therapy.<sup>7, 8, 9</sup> Chart 1 illustrates the averages of absolute lymphocytosis among the four groups of patients, with weekly changes after serum therapy or after admission among the controls. Chart 2 illustrates the findings in a group of seventy untreated patients followed from the inception of the disease.<sup>10</sup> Initial counts among our controls are lower than in the treated cases, this being due, we feel, to the fact that the control series contained more of the mild cases. In general, the degree of lymphocytosis correlated well with the number and severity of paroxysms, the higher counts accompanying the more severe symptoms. The charts agree well with the studies previously mentioned in that significant decreases in lymphocyte counts occurred within one to two weeks following serum therapy at periods of the disease in which rising counts would ordinarily be anticipated. However, these decreases, though very marked in some instances, did not correlate at all with significant lessening of paroxysms or vomiting, even among the few patients that could be classed as improved.

One further study was made in an effort to obtain more objective evidence of the effect of serum therapy in relation to the course of disease, this consisting of agglutination studies in several of the untreated and many of



the treated patients both before and at frequent intervals following treatment. The accompanying Chart 3 illustrates these findings.

A very good titer rise is apparent within twenty-four hours of any type of serum therapy, with rapid falling off among the horse and human serum treated cases, but with maintenance of better titers than among the controls in all treated cases for at least two weeks after serum treatment. Titers drawn in the third and fourth weeks of the paroxysmal stages must represent not only passively transferred antibody but also the patients' own active production of antibody at this stage of disease, as shown among the controls which have the expected titers at this period, but in lower concentration than the treated cases.

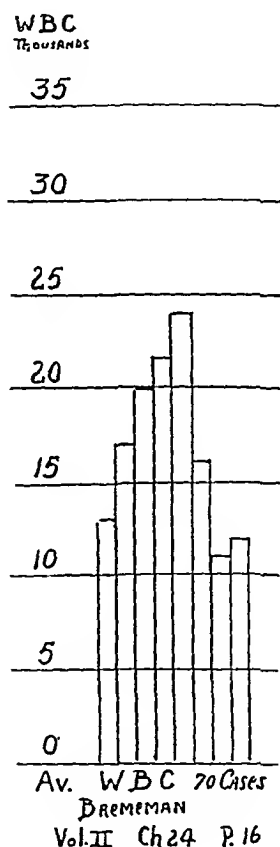


Chart 2.

In analyzing individual cases, it was evident that the higher initial titers were present in the milder forms of the disease, and that these generally responded with a higher titer rise following serum treatment. Patients who were given the larger doses of serum generally had the higher agglutination rises, but there were several instances in which relatively small dosage of any of

the types of sera resulted in significant immediate and sustained agglutination titer rises. In no instance was it clear that definite improvement occurred among those patients with excellent agglutination responses, and as a matter of fact most of those who were judged improved had average or slightly lower than average agglutination responses.

Titre

1-500

1-320

1-160

1-80

1-40

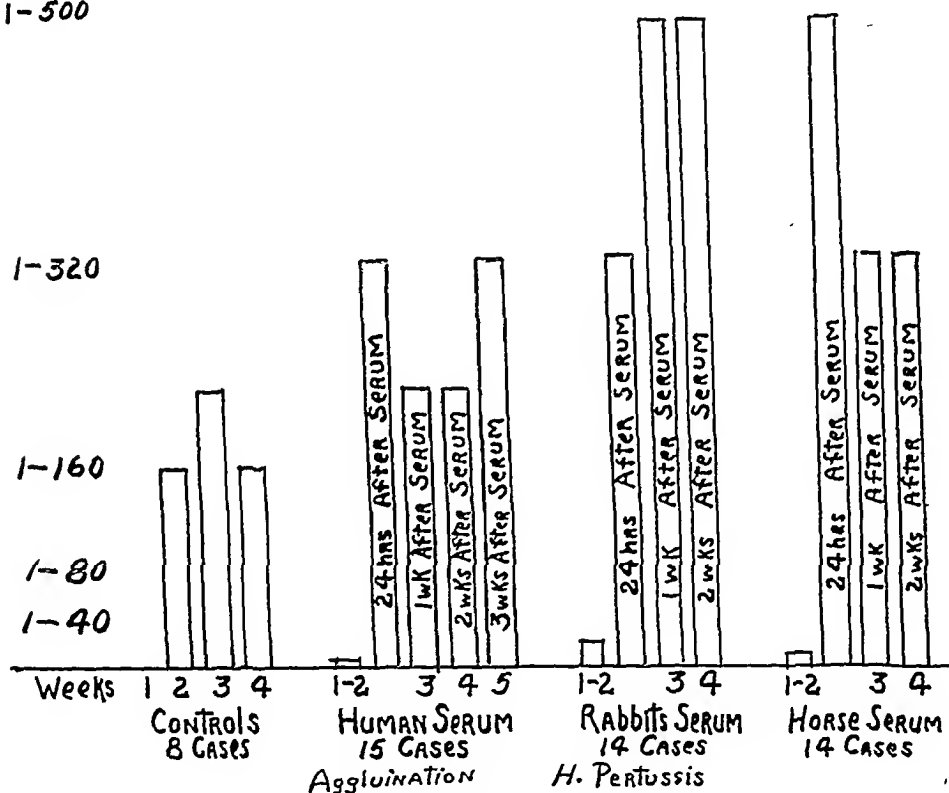


Chart 2.

Scheinblum and Bullowa,<sup>5</sup> using hyperimmune serum, found no correlation between response to therapy and height of post-treatment titers. Bullowa and Alterman<sup>11</sup> used rabbit antitoxin in treatment and found no definite improvement despite marked rise in serum antitoxin titers. Ketsampes and associates<sup>7</sup> found significant titer rises in twenty-two patients treated with hyperimmune human serum, but did not state specifically whether the degree of titer response could be related to the course of the patient.

Weights on all patients showed no significant variations among the treated and controls. Practically every patient gained weight while in the hospital, weight gains becoming evident almost invariably shortly after the peak of disease was reached, as would be expected in the absence of refractory complications.

Complications included pneumonia, otitis media, diarrhea, malnutrition, anemia, and two instances of transfusion malaria. Pneumonia occurred with about the same frequency in the four patient divisions, averaging 15 per cent. Only one case of pneumonia developed following serum treatment, this occurring in the rabbit serum-treated group one week following the serum. Pneumonia did not develop among any of the control patients during hospitalization. The remaining complications occurred in insignificant numbers. Of these, all but the cases of transfusion malaria were present on admission. Sulfonamides, penicillin, transfusions, parenteral fluids, and other indicated supportive therapy were used as necessary among the four groups of patients with uniformly satisfactory responses.

#### DISCUSSION

It is difficult to ignore the large numbers of favorable reports on the use of hyperimmune serum in whooping cough. These have been reviewed by Felton,<sup>12</sup> Kohu et al,<sup>13</sup> and recently by Brainerd<sup>9</sup> and Rizzo.<sup>14</sup> Combining figures of human serum treated cases in which patients are separated by age groups with respective mortalities, a total of 784 patients is obtained, of whom 445 were less than one year of age, with a mortality in this group of 2.4 per cent. In various groups reported mortalities ranged from none in smaller series to as high as 20 per cent in a group in which all had bronchopneumonia. The largest series is that of McGuinness and associates<sup>15</sup> in which the mortality rate among 236 patients less than one year of age was 2.1 per cent. Five hundred seventy-two or 73 per cent of the 784 patients were considered definitely improved by the serum. The range of patients considered improved within a few days to a week after administration of the serum in the various groups was 63 per cent to 88 per cent.

Relatively few reports on the use of hyperimmune rabbit serum have been published.<sup>13, 16, 17, 18</sup> Favorable results were noted in only one group, that of Beaudet,<sup>16</sup> the others reporting equivocal results. Becker<sup>21</sup> treated sixteen children in the incubation stage and twenty-five in paroxysmal stage with horse antitoxin from the Behring works. Ten of the incubation-stage cases developed the disease and there was no apparent effect of therapy in the twenty-five cases.

The great majority of the aforementioned reports have stressed the role of serum therapy in diminishing the mortality in the youngest age groups, as compared with similar cases seen in previous years. Mortality rates among nonserum treated cases in the age group under one year actually vary widely, these having been reported as low as 4.9 per cent and as high as 25 per cent.<sup>13, 19</sup> Chart 4 shows the mortality in the youngest age group at this hospital from 1930 to 1946, and aside from an actual mortality rate of 6.4 per cent during the years 1940 to 1945, a fairly steady decline in mortality has been notable since 1937. This coincides with the picture of over-all mortality changes occurring in Boston among all age groups beginning in the year

1936, as illustrated in Charts 5 and 6. It is to be noted that this change antedates the general introduction of the sulfonamide group of drugs and might well indicate declining severity of the natural disease, at least in this area.

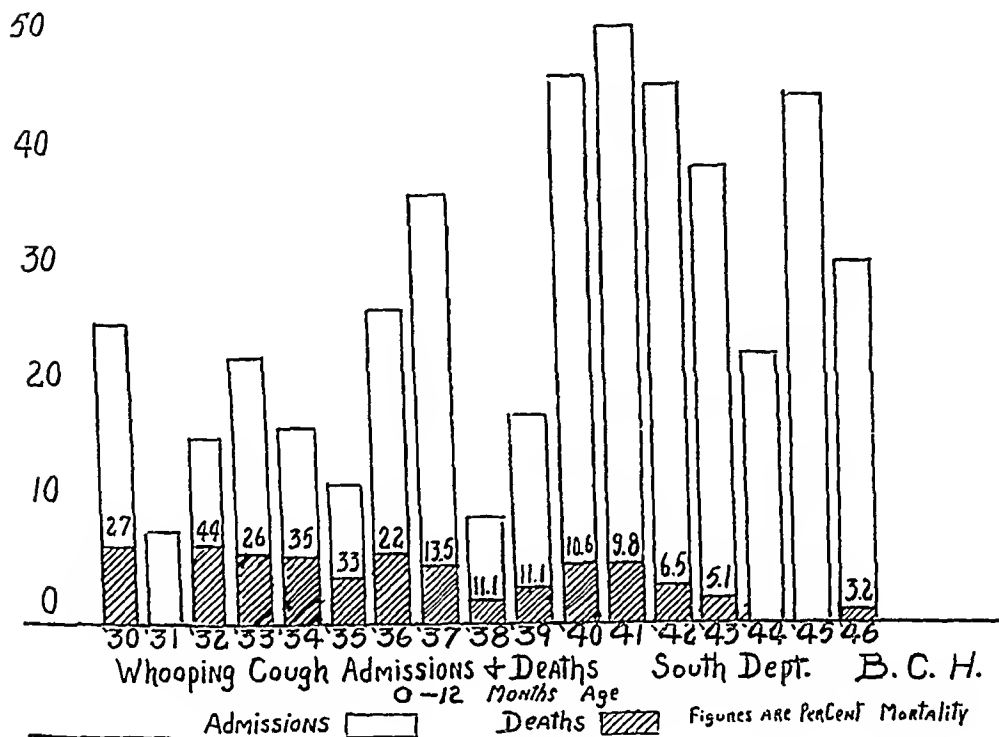
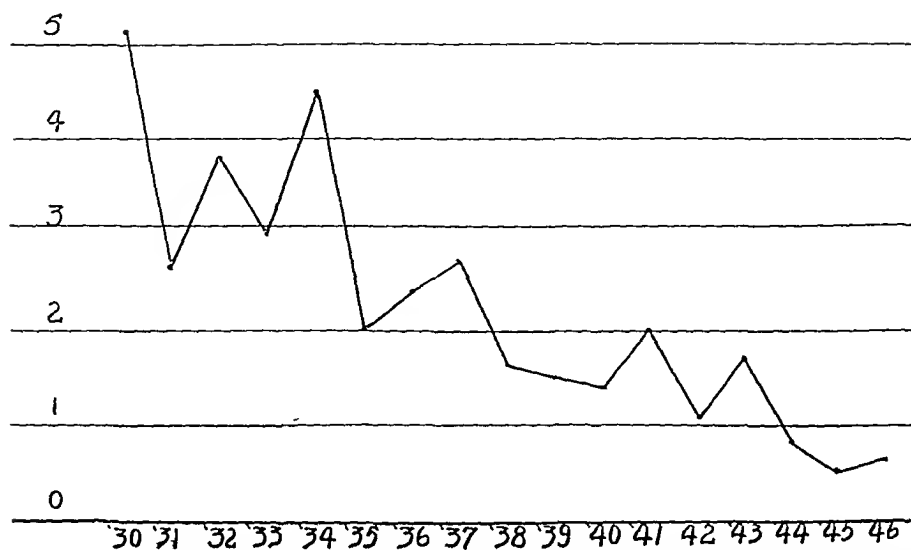


Chart 4.

Admittedly, any evaluation of a single therapeutic agent against pertussis is extremely difficult because of the marked natural variations in the severity as well as duration of the disease. Critical appraisal of results must then become especially difficult if other agents known to be effective against the most common and very serious complications of the disease are used concomitantly. Thus, antibiotics could not well be withheld in a patient seriously ill with a pulmonary complication of pertussis, and since the latter cause by far the greatest number of deaths in the disease, lowered mortality rates among patients treated with both an antibiotic and an immune serum could not easily be attributed to the latter. Thus, Frank and associates<sup>20</sup> found a mortality rate of 20 per cent in thirty consecutive patients with whooping cough with bronchopneumonia treated with human hyperimmune serum alone. The same authors found a mortality of 4 per cent in seventy-seven consecutive patients with similarly complicated cases treated with sulfathiazole alone. One might easily imagine a further reduction of this mortality if penicillin had also been available for pneumonia-producing organisms resistant to sulfonamides. In view, then, of the widely varying mortality figures on

Per. 100,000



Whooping Cough Deaths All Ages—Boston (Per. 100,000 popul.)

Chart 5.

## Deaths

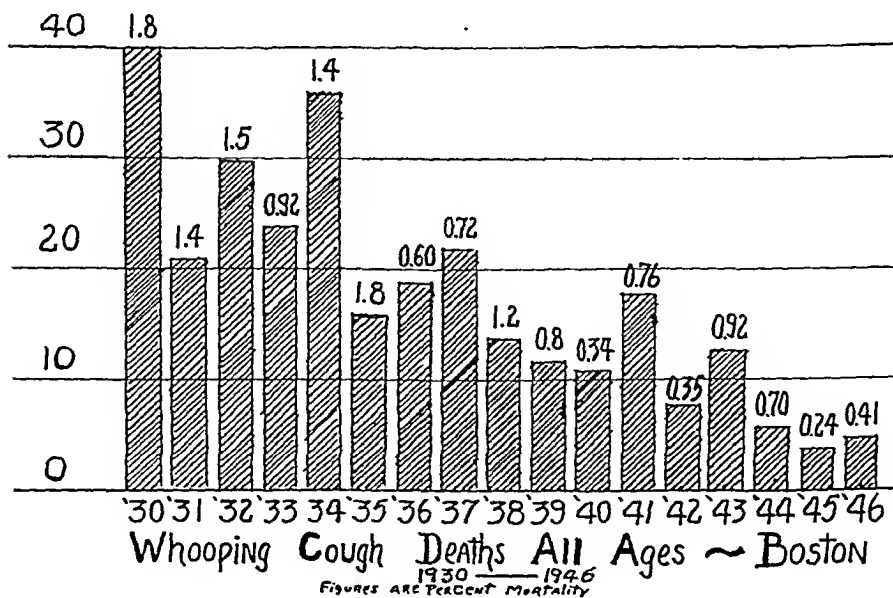


Chart 6.

whooping cough in different clinics and in the years before and after the antibiotics came into general and liberal use, extreme caution is indicated in the evaluation of any antipertussis agent based on lowering of previous figures.

Further evaluation of serum therapy as noted in previous reports has rested on impressions of marked reduction in coughing and vomiting and on improvement of the general condition of the patient. In very few of the studies was actual day-to-day charting of the frequency and severity of paroxysms carried out because of limitations of time and personnel and also because many of these patients were cared for at home. Even had this procedure been carried out, definite conclusions could not necessarily be drawn in the absence of adequate numbers of controls. Thus, in our own group of forty-eight hospitalized controls whose paroxysms, whoops, and vomiting were charted from day to day, it was often noted that several of these showed striking improvement in a given forty-eight hour period either early or late in the disease. Had serum been given just prior to one of these spontaneous changes, erroneous conclusions as to serum effect could easily be drawn.

The fact that pulmonary complications have very rarely been seen following serum therapy has also been stressed as an indication of the effectiveness of serum. Our study does not indicate this to be necessarily due to serum therapy, since none of the controls developed a pulmonary complication after hospitalization.

Multiple dose serum therapy has been used in the large majority of reported cases, but evidence that this is more efficacious than single large doses has not been advanced. It appeared logical to assume that if no demonstrable clinical effect could be obtained with a single large dose, which, in over 90 per cent of our cases, was equivalent to the total multiple dose treatment recommended, i.e., 60 c.c. of the hyperimmune serum or 7.5 c.c. of the concentrated globulin fraction thereof, then further efforts along this line would not be expected to show any great difference. If prompt and significant agglutination titer rises, together with a fairly rapid fall in the total number of circulating lymphocytes, are considered an index of adequate serum therapy, then these criteria indicate results equivalent to those previously reported with multiple dose therapy where these factors were utilized as a more objective index of response to serum treatment.<sup>7, 8, 9, 11</sup>

#### CONCLUSIONS

1. One hundred fifty consecutive hospitalized patients with pertussis in the period October, 1946, through December, 1947, were studied with a view to evaluation of various types of specific serum therapy. Thirty-eight patients received horse serum, thirty-three a hyperimmune rabbit serum, thirty-one human hyperimmune serum, and forty-eight patients were used as controls.

2. There were no deaths in any of the four groups.

3. On the basis of day-to-day charting of paroxysms and vomiting, weight changes, and general appearance of patients, no significant differences in the clinical courses of any of the patient groups was evident.



4. Significant reductions in absolute lymphocytosis as well as good rises in serum agglutination titers followed serum therapy, but these changes did not correlate with clinical improvement.

5. The number of both treated and control cases is admittedly quite small, but in view of the currently held ideas as to the value of human hyperimmune serum therapy, it is felt that this study suggests the need for further more critical and controlled evaluation of the serum treatment of pertussis.

6. The lack of fatalities, though possibly influenced by serum, is more likely the result of improved therapeutic procedures relating particularly to bacterial complications and to diligent nursing care.

The authors are indebted to Drs. Alexander Tersin, Lecturer in Bacteriology, Central Institute of Hygiene, Belgrade, Yugoslavia, and Lawrence Kilham of the Department of Bacteriology of the Harvard Medical School for agglutination and cultural studies necessary to this report, and to the nursing staff of the South Department, whose great interest and cooperation were indispensable to this study.

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## EPIDEMIC DIARRHEA OF THE NEWBORN INFANT

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THERE are inherent dangers in the preparation of formula for infants. The young baby is particularly susceptible to intestinal upsets, either infection or toxæmia. In the scheme of things every baby, human or animal, should have its mother's milk. Nature provides a safe and fresh food supply in the maternal milk. If, on the other hand, we are to tamper with nature, the most rigid safeguards must be applied to the procedures of formula preparation.

These procedures should be of such a character that the day-old refrigerated food will be practically free from bacteria as determined by bacteriological culture methods. To secure this result regularly and with certainty, the formula nurse must have a knowledge of the techniques of both bacteriology and mechanics, aseptic technique and refrigeration operation.

While it is not the purpose of this paper to relate the history of infant diarrhea, it should be appreciated that in recent years great progress has been made in the control of the disease. Less than fifty years ago, one-quarter to one-third of all infants died during the first year of life. About 80 per cent of these deaths were due to "cholera morbus" or infant diarrhea. The season of greatest prevalence was during the summer months. Forty years ago the public milk supply in Washington, D. C., had an average bacterial count of 10,000,000 per cubic centimeter; today the counts are about 5,000 per cubic centimeter, a reduction of almost 100 per cent.

It was Nathan Strauss who, about the middle nineties, led the campaign for the establishment of safe milk stations for babies. But it was not until about thirty years later that he said, "I have finally won my fight for safe milk for babies." Today only about fifty infants per 1,000 die in the first year of life compared to 300 fifty years ago. All of which means that now the death rate has been reduced by over 80 per cent, or stated another way, out of every 1,000, 250 babies under one year of age are being saved annually.

In Washington, D. C., where we had 27,000 births in 1947, the lives of almost 7,000 babies were saved compared to the rate of fifty years ago. This yearly addition to the population gives something to ponder. But our interest here is the control of infant diarrhea in hospital nurseries. Observation over the last twenty years indicates that there may be two types of infant diarrhea. The numerous outbreaks of the 1930's were highly explosive in character; within a week or less, one-third or more of the infants would develop the infection. There was a high case mortality of 30 to 40 per cent. The

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disease had a sudden onset with excessive diarrhea and rapid dehydration. These outbreaks were sudden, severe, and of short duration.

An investigation undertaken in 1936 of twenty-four-hour-old bottled baby food in six of our local hospitals showed that the average bacterial count per cubic centimeter was almost 500,000, with 24 per cent of the specimens showing *Bacillus coli* contaminations; that the drainage water from the nipple container carried an average of 60,000 bacteria per cubic centimeter, and that the bottles, after having been "washed and sterilized," each carried a load of about 80,000 bacteria.

While the excessive bacterial counts in the bottled milk were not of themselves directly the cause of infant diarrhea, it at once became apparent that they kept the door open for the introduction of dangerous disease-producing organisms or viruses. The high counts prevailed continuously; an epidemic arose only when the etiologic factor was introduced from an adult carrier or other source into the bottled milk, thence spreading throughout the formula laboratory equipment.

The severity of these outbreaks during the thirties might well have been due to multiple massive doses of the causative agent in the bottled food. Since 1940, however, the formula laboratories have been well organized with counts of not more than several hundred bacteria per cubic centimeter at any time. Yet we have had several low-grade outbreaks.

Such an outbreak occurred in 1946 in a hospital in which the total deliveries for the year were 4,166. During a three-month period, there were 128 cases of diarrhea among the newborn, with but four deaths, a very low case mortality rate. In contrast to the epidemic of the 1930's, the 1946 outbreak was characterized by its mildness, its gradual onset, and prolonged duration.

Simultaneously with this infant outbreak there was a widespread epidemic of contact adult diarrhea in that section of the city where the hospital was located. Based on the number of these patients treated in outpatient clinics and those treated by private physicians, it was roughly estimated that there were about 10,000 adult cases.

The first case of infant diarrhea in the hospital during the 1946 outbreak was that in an infant born to a mother convalescent from contact diarrhea. The incubation period in the infant was two days. Within a few days there were secondary cases, all of whom were isolated. But new cases in two-day-old babies of mothers having diarrhea continued to occur from time to time; from these there were secondary contact cases. This process of introduction, spread, and isolation continued over a period of three months and involved 128 infants.

As had been the routine for a number of years the formulae were frequently checked for bacterial contamination, and, during the epidemic period, the bottled food continued to be practically sterile. There appears to be no doubt that there were secondary cases among the infants. How many is not known. These were, however, contact cases and not foodborne.

An interesting question here is whether or not the safety of the bottled food protected the nurseries from a highly fatal virulent epidemic of diarrhea. One might theorize on this question without a conclusion. But here the point is that the 1946 epidemic was low-grade, almost nonfatal, while the epidemics of the 1930's were explosive and virulent with a high mortality.

#### TECHNICAL ERRORS

A number of technical errors were observed during the early days of this survey, and any one of these may lead to dangerous contamination of bottled food. In the first place inadequate washing of bottles was of frequent occurrence. As already stated "washed and sterilized" bottles had an average bacterial count of 80,000 per bottle. It was then found that by thorough washing and rinsing, heavy contamination could be reduced as much as 90 per cent. Today with modern detergent powders, bottles can be rendered practically free from bacteria; they are bright, crystal clear, and free from film.

There was, secondly, the practice of piling bottles in a large pan two-thirds full of water while the bottles filled the vessel. Many were not in contact with the water. As a formula laboratory procedure steam "sterilization" is wholly inadequate. There is but one safe and dependable way to sterilize bottles—in the autoclave.

A third hazardous practice was that nurses in training were permitted to perform the technical procedure of preparing food by formula.

A fourth defect related to the use of warm stock water in making the formulae. When this investigation was started in 1936, it was the universal practice to use warm stock water. It was contended that it was more convenient to sterilize the water the morning of the day it was used, and then too, it was argued that powdered foods went into solution more readily in warm water.

It was found by automatic recording of the refrigerator temperature that when 200 bottles with their warm content were placed in the refrigerator (recording a temperature of 45° F.) there was a gradual increase for six hours to 78° F.; and during the following seven hours there was a slow drop to 45° F. Thus for thirteen hours a temperature prevailed favorable to the growth of bacteria, perhaps dangerous ones. This accounts in part for bacterial counts of over a million per cubic centimeter in twenty-four-hour bottles.

The correction here was simple: merely sterilizing gallon containers of water in the autoclave the day previous, allowing these to cool to room temperature and finally placing them in the refrigerator overnight. The use of this cooled stock water for formula provided continuous refrigeration of the bottled food. Thus bacterial multiplication was inhibited.

A fifth hazard was the neglect of defrosting. This occurred especially when there was a frequent turnover in the personnel of the formula room. It is now required that the refrigerator temperature be recorded daily at 9 A.M. and 1 P.M.

A sixth hazardous difficulty was mechanical failure of the refrigerator equipment. In 1938 there was an outbreak of infant diarrhea in one of our hospitals. On investigation, it was found that the formula nurse was gowned, capped, masked, and gloved. This created a sense of security, but behind the scene it was found that the stock water was not chilled and that the empty refrigerator registered but 72° F. Many of the 24-hour formula samples had bacterial counts of over one million bacteria per cubic centimeter. The refrigerator was replaced and the stock water chilled, with the result that the bacterial counts dropped to a few per cubic centimeter.

A seventh hazardous procedure dealt with multiple formula rooms. A revolutionary change in social custom concerning childbirth occurred especially during the 1930's. The number of hospital deliveries increased by several hundred per cent. With increasing numbers of deliveries, the hospital increased the number of wards, and strange to relate, there was a corresponding increase in the number of formula rooms. These multiple rooms with their lack of good aseptic and sterilizing procedures, the use of nurses in training with no set standard of bacteriological technique, and a changing personnel, led to high bacterial counts and a multiplying possibility of toxiosis or infection by indirect contact through food. By consolidating these operations in a central laboratory in each hospital, there was not only greater economy but there was also established a uniformly high standard in procedure.

As an example of the above situation, and this was no exception, at one hospital there were 598 deliveries in 1930 and 2,028 in 1940. With this increasing number of deliveries and wards, the number of formula rooms was increased to three. During that period there were three separate outbreaks of diarrhea. By 1940 there was established a single formula room operated under a standard aseptic procedure. Since that time the day-old formulae have been practically sterile and despite the 4,028 deliveries in 1947, the nurseries have been free from epidemic diarrhea and impetigo. In a general way the above applies to the other six supervised hospitals.

#### STANDARD FORMULA ROOM PROCEDURES

The following procedure for preparing formula may be designated "The Chilled Method of Preparing Formula":

1. Autoclave all equipment, including all the nipples. Protect nipples from contact with container by wrapping in toweling.

2. Autoclave formula stock water, cool to room temperature, and chill overnight in refrigerator.

3. Record temperature of refrigerator at 9 A.M. and 1 P.M. Temperature should be set at 40° to 45° F. and at no time should go above 50° F.

4. It is desirable that the formula nurse should not be required to prepare the bottled food by more than three different formulae.

5. Practice good bacteriological laboratory technique in preparing and bottling the food. And at least once a week culture six to ten 24-hour formulae to check the effectiveness of the aseptic procedures and refrigeration.

6. Experience indicates that bacterial counts of 24-hour formulae should not be more than 500 per cubic centimeter and no single count should be more than 10,000. Good procedure gives counts of less than 5. Counts over 100,000 are a danger signal indicating errors in aseptic or mechanical procedures. Counts of 1,000,000 or over point to a possible outbreak of infant diarrhea.

A recent procedure for rendering the formulae safe for infants is that of autoclaving the bottled food, after having been nipples and capped, by the high pressure—low temperature method. This autoclave equipment is now on the market. It is used in two local hospitals, and in over 500 samples of formulae so prepared over 99 per cent were sterile.

#### CONCLUSIONS

1. In either large or small hospitals, any one of the several technical errors here related may lead to a serious epidemic.

2. If errors are eliminated and the day-old formulae are practically sterile, there is no danger of an explosive, fatal, foodborne outbreak.

3. If the formulae are aseptically prepared, any infection introduced into the nursery may be spread by contact, but these cases will be mild and of low virulence.

4. The formula room procedure should be checked weekly by bacteriologic examination of day-old food.

## BOTULISM AND TICK PARALYSIS

### IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE BULBAR POLIOMYELITIS

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**P**OLIOMYELITIS occurs throughout the United States at the present time in endemic proportions throughout the year, and increases to epidemic incidence in certain localities in the middle and late summer months. The bulbar type of this disease is seen usually in isolated cases, but again in certain epidemics this type has been predominate. Bulbar poliomyelitis, as the name implies, is reserved for that type of the disease in which the cranial nerves arising from the medulla oblongata and pons are involved. It is, however, loosely applied to any case of poliomyelitis in which there is cranial nerve involvement.

In the last twelve-month period two cases of clinically diagnosed bulbar poliomyelitis which have been referred to this hospital for diagnosis and treatment have been extremely interesting and are worthy of reporting.

#### CASE REPORTS

**CASE 1.**—G. B., a 10-year-old white girl, entered Doernbecher Hospital Nov. 15, 1947. The child was referred here from Redmond, Ore., as a bulbar poliomyelitis patient with the complaints of double vision, difficult breathing, flaccid neck and extremities, stomach-ache, and vomiting.

**Family History.**—The family, consisting of the father, the patient, and two younger siblings, lived with a rancher and his wife. They ate at a common table and used home-canned foods. The father could not recall any foods eaten Nov. 13, 1947, except hamburger and potatoes. No other members of the family group were ill; however, the father stated he could not get his eyes to focus, and that he saw double that evening. The city physician was called and agreed to examine the father at that time.

**Present Illness.**—Upon arising on the morning of Nov. 14, 1947, the patient complained of seeing double and shortly thereafter complained of abdominal pain. She ate a light breakfast and returned to bed as she did not feel well. She vomited at 10 A.M. and again at 1 P.M. and became progressively weaker and flaccid. That evening she continued to vomit, was unable to swallow, and was unable to move herself voluntarily. She was incontinent of urine and choked on mucous accumulations in the pharynx during the night. She was taken to a physician the following morning; he did a lumbar puncture and arranged to have the child sent here as a bulbar poliomyelitis patient. She was transported 250 miles by ambulance to this hospital, receiving oxygen by nasal catheter en route. She arrived here on the evening of November 15, having been entirely without fluids for the previous twenty-four hours.

**Physical Examination on Entry.**—Examination revealed a dehydrated, slender, 10-year-old white girl with a flaccid paralysis of all extremities, back, and neck. She was unable to talk or swallow, although she could whisper

From the University of Oregon Medical School and Doernbecher Children's Hospital.

very faintly and with great effort. Her color was ashen. She complained of no pain. Temperature was 97° F., blood pressure 155/105, respiration 30 and very shallow. The patient was fully conscious, and would blink, and attempt to whisper replies. The upper eyelids could only be raised about halfway. The conjunctiva were injected and there was a slow, lateral nystagmus present. The pupils were 3 mm. round and equal, and did not react to light or accommodation. Funduscopic examination was negative. Expression was limited to a faint grimace and smile. The mucous membranes of the mouth and pharynx were dry, and the pharynx was filled with thick, tenacious mucus. The tongue could not be moved, and the gag reflex was absent. The diaphragm was high, and respirations were shallow, regular, and entirely intercostal in type. Examination of the chest and abdomen was otherwise negative. The extremities were symmetrical, very slender, and entirely flaccid. They could not be moved against gravity but were moved feebly on command. The patient could be flexed into any position with ease. Reflexes were entirely absent. Kernig and Brudzinski were negative. The genitalia were normal except that the vaginal introitus was gaping. Rectal tone was decreased and two fingers were inserted into the rectum without resistance. Sensory examination could not be evaluated.

*Laboratory Examination.*—Spinal fluid was clear, Pandy negative, pressure would not register on the manometer, and the cell count was 3 lymphocytes. White blood count 28,150 with differential of 69 per cent neutrophils, 12 per cent staff cells, 17 per cent lymphocytes, and 1 per cent monocytes. Blood sugar was 90 mg. Alkali reserve was 62 volumes per cent. Blood culture was negative.

*Hospital Course.*—The patient was placed in Trendelenburg position, parenteral fluids and nasal oxygen were started. At 6:30 A.M., Nov. 16, 1947, respirations ceased; she was maintained with artificial respiration until transferred into a respirator. That afternoon a tracheotomy was performed with the patient in the respirator. The patient was still conscious and would reply to questions by blinking her eyes twice for "yes" and once for "no." Large quantities of mucus were aspirated from the trachea, and she would develop sudden respiratory embarrassment with cyanosis. Bronchoscopy through the the tracheotomy opening was done frequently, averaging twice a day for the first two to three weeks. Large crusts, which often completely occluded one of the main-stem bronchi, were removed with foreign-body forceps. The patient remained in the respirator for seventy-one days. A brief résumé of this course will be presented.

By Nov. 21, 1947, the patient had become less responsive; it was noted that on bronchoscopy exudate was presenting itself into the upper portion of the right main-stem bronchus, and it was felt that she had developed a right upper lobe pneumonia. Word was received that day that the father had expired at the city isolation hospital of an acute bulbar paralysis.

By Nov. 23, 1947, facial expression had gradually failed and the patient could not open her eyes, blink, or smile. The pupils were dilated and did not react to light. The patient was maintained on intravenous and subcutaneous fluids in addition to tube feedings and prophylactic penicillin. Pathologic report reveals that the diagnosis of poliomyelitis could not be substantiated as the cause of death in the father. It was decided at this time that the child should be given Botulinus antitoxin. The antitoxin was obtained on November 27 and three injections of 10,000 units each of Anti A and B Botulinus antitoxin were given at four-hour intervals. Following the last injection the patient developed a generalized urticarial rash and angioneurotic edema of



the face. This reaction responded to adrenalin but further administration of antitoxin was not felt justified. On November 28 it was demonstrated that the patient had a bilateral sixth nerve paralysis. On December 1 facial expression was returning and she was able to move the extremities to a slight degree. The patient was able to swallow liquids without the Levine tube on Jan. 12, 1948. For the first time the patient was able to remain out of the respirator on Jan. 17. She remained out with encouragement for forty minutes. Two days later she remained out for forty-eight hours. She was gradually completely removed from the respirator in the following week. She could not cough up secretions and tracheotomy was maintained for aspiration. She was exercised daily in the Hubbard tank, and regained strength and weight rapidly. The tracheotomy tube was removed Feb. 10, 1948, having been in place for eighty-five days. The wound closed in four days. She was discharged from the hospital February 17, at which time she still had practically complete loss of movement of both leaves of the diaphragm, and complete loss of accommodation. She was fitted with glasses for near vision.

The Public Health Service reported demonstrating botulinus organisms from the scrapings recovered from the dishes used by this family group on November 13.

No report has been found in the literature of a patient with botulism who has survived after having developed a complete pharyngeal paralysis. Certainly this patient would have succumbed if it had not been for the respirator, tracheotomy, and constant nursing and medical attention.

Correspondence with the patient nine months following her recovery reveals she is well, rides a bicycle, participates in games, and uses her glasses only for reading.

CASE 2.—R. G., a 5-year-old white girl, entered Doernbecher Hospital July 19, 1948, with a complaint of paralysis. Family history was noncontributory.

*Present Illness.*—July 15, 1948, the mother noticed the child persistently stumbled when she walked, and the following day she was unable to walk except by holding on to objects. On July 17 she had difficulty in swallowing and complained that her throat hurt. The following day she was unable to walk, talk, or hold her head up. She had no respiratory difficulty and did not complain of pain. She was examined by a physician and referred into Doernbecher Hospital as a bulbar poliomyelitis patient. Physical examination on entry revealed a well-developed, well-nourished white girl who was flaccid in all extremities, back, and neck. She could not move her head and could not talk. Temperature was 99.6° F. (R), blood pressure 108/72. Respirations were rapid, irregular, and predominantly diaphragmatic. The skin was pale and dry, the mucous membranes were dry. She was unable to swallow fluids and the gag reflex was absent. The chest and abdomen were negative. Extremities were completely flaccid with loss of all reflexes.

*Laboratory Examination.*—Spinal fluid was clear, Pandy negative, cell count 8, total protein 20 mg. per cent, culture negative. White blood count was 28,000 with differential neutrophils 57 per cent; eosinophils 2 per cent; lymphocytes 11 per cent; monocytes 1 per cent; basophils 1 per cent; staff cells 28 per cent; sedimentation rate 2/10; serology negative.

This case was presented briefly on morning rounds, July 20, 1948, as an atypical poliomyelitis patient with bulbospinal involvement manifesting flaccidity, negative spinal fluid, leucocytosis, and no temperature elevation. With a strong recollection of Case 1 in this paper, the parents were again contacted

and questioned, particularly as to the type of food recently eaten and health of the remainder of the family group. This interrogation was negative and the patient was re-examined. Findings at that time were essentially as recorded on entry; however, respirations were more impaired and the patient was showing mild cyanosis. A careful search was made for a tick, and the latter was found lying under a thick mass of hair over the left parietal area. On closer examination the tick was engorged, measuring 10 mm. in length, 7 mm. in transverse diameter, and 3 mm. in depth. An area of scalp with a radius of 2 cm. about the attachment of the tick was covered with fecal material which had the appearance of coarse pepper. The tick was removed by an elliptical incision of the scalp removing the area of attachment of the tick.

*Hospital Course.*—On the following morning, July 21, the patient was definitely improved, color was good, limbs were moved voluntarily, and she was taking oral fluids. On July 23 the patient was sitting up in bed, talking, and eating well. She was extremely uncooperative, and physical examinations could not be too well evaluated. The white blood count had dropped to 11,000. The patient was walking on July 24, afebrile and entirely recovered. She was discharged that day.

The tick in this case was *Dermacentor variabilis*, or the dog tick.

#### SUMMARY

1. Two patients manifesting bulbar paralysis are presented, each of which have been initially considered to have poliomyelitis.

2. These two cases demonstrate the necessity of summarization of all laboratory, clinical findings, and, if these are not in agreement with the diagnosis of poliomyelitis, further search is indicated.

# ROENTGEN MANIFESTATIONS OF INFANTILE HYPERTROPHIC PYLORIC STENOSIS

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## INTRODUCTION

DESPITE the prominent role of radiology in the recognition of gastrointestinal disorders, comparatively few pediatricians, surgeons, and radiologists fully appreciate the value of roentgen methods in the diagnosis of infantile hypertrophic pyloric stenosis. This may be explained by the fact that certain roentgen criteria proposed many years ago have been found unreliable for this condition.<sup>1, 2</sup> Also, there are many clinicians who are hesitant to utilize the procedure in infants for fear of possible harmful effects.<sup>3, 4</sup>

The purpose of the following study is twofold. First, newer, more specific roentgen signs are emphasized and their value determined in an unselected series of cases in the manifest stage of infantile hypertrophic pyloric stenosis. Second, information as to the presence of residual pyloric changes was obtained by roentgenologic follow-up studies ranging from five months to twenty-two years after successful surgical treatment by the Fredet-Ramstedt operation.

## CLINICAL CONSIDERATIONS

The clinical features of hypertrophic pyloric stenosis have been adequately described in many excellent reports and will not be elaborated upon here.<sup>5</sup> It may suffice to state that palpation of the pyloric tumor is generally considered to be the most important clinical sign. Though experienced observers have claimed that this may be possible in practically all cases,<sup>1, 6</sup> other qualified clinicians have been unable to demonstrate a palpable mass in more than two-thirds of cases.<sup>1, 7</sup> It has been our observation that in some instances competent physicians were at variance in their opinion as to the presence or absence of a tumor. Also cases have been reported in which a mass was thought to be present clinically, but in which a normal pylorus was subsequently demonstrated at operation.<sup>4</sup> The occurrence of these cases makes it desirable to utilize methods which may improve the accuracy of clinical diagnosis.

## ROENTGENOLOGIC CONSIDERATIONS

Earlier roentgen studies of hypertrophic pyloric stenosis placed much emphasis on such signs as gastric hyperperistalsis, dilatation, and retention as important features in the establishment of a correct diagnosis.<sup>8, 9</sup> These signs cannot be considered as specific since any of them have been found to occur

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Fig. 1.

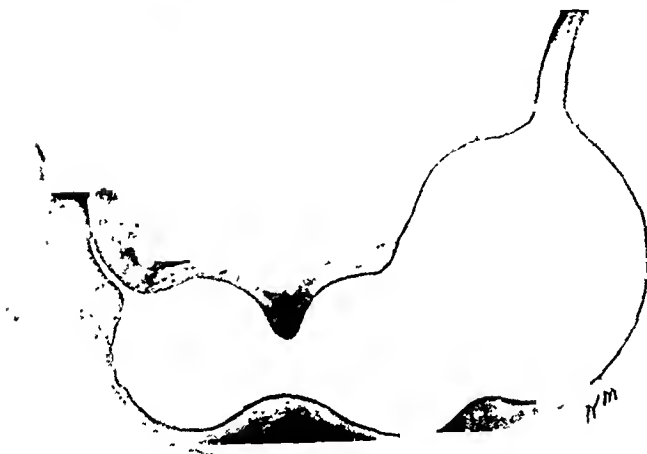


Fig. 2.



Fig. 3.

*nmackley*

Fig. 1.—The pathologic changes of hypertrophic pyloric stenosis. Marked obstruction prevents filling of the pyloric channel.

Fig. 2.—A small amount of barium has entered the narrowed pyloric channel, the "string sign."

Fig. 3.—The pyloric tumor encroaches upon the lumen of the pyloric channel and protrudes into the base of the duodenal cap.

in such conditions as gaseous distention of the intestines,<sup>10</sup> severe infection, cerebral trauma, and duodenal atresia.

The modern criteria for the radiologic diagnosis of infantile hypertrophic pyloric stenosis were introduced by Meuwissen and Slooff in 1932.<sup>11</sup> Subsequent articles in the European and American literature have served to corroborate their findings.<sup>12, 13</sup> In all these studies an attempt was made to demonstrate the radiologic equivalent of the underlying anatomic changes.

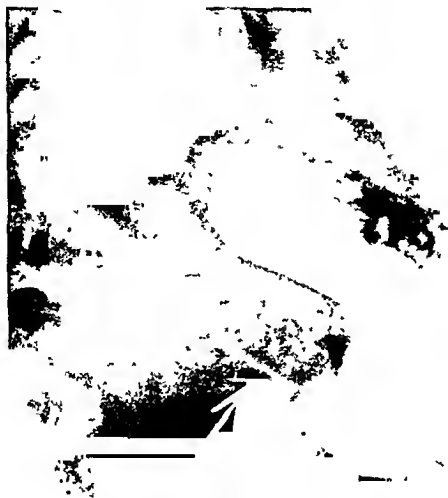


Fig. 4.—Typical "string sign."

It will be remembered that the pathology of this condition consists of a hypertrophy of the pyloric muscle which enlarges to involve not only the true pylorus but also the prepyloric segment of the stomach, the so-called "canalis egestorius." Mucosal thickening further diminishes the caliber of the lumen. These anatomic changes result in the formation of a narrow canal at the junction of the stomach and duodenum. The direct demonstration by barium studies of this narrowed segment forms the basis of current x-ray diagnosis. On proper filling the stenotic canal will be outlined by a thin streak of barium measuring usually 2 to 3 cm. in length. This radiologic pattern is commonly referred to as the "string sign" (Figs. 2 and 4). To our knowledge, this radiologic sign has not been observed in any other gastric lesion of infancy and should be considered as pathognomonic. In markedly obstructed cases it may be difficult to demonstrate the stenotic canal, but by proper manual compression its most proximal portion can frequently be visualized at the height of a peristaltic wave. A short streak of barium, having the contour of a bird's bill, may then protrude from the distal part of the pyloric antrum, the so-called "pyloric beak" (Fig. 5).

A second valuable radiologic sign is the indentation of the base of the duodenal cap (Figs. 3 and 6). The structural basis for this feature is the cervixlike protrusion of the pyloric tumor into the lumen of the proximal

duodenum. Contrary to the findings of Miller and Ostium<sup>10</sup> that changes in the duodenal cap were not observed by them, we have found indentation of the base of the duodenal cap to be of appreciable value.



Fig 5—A minimal amount of barium has penetrated into the proximal portion of the pyloric channel, the "pyloric beak."



Fig 6—S, String sign, I, Indentation of proximal duodenum.

## TECHNIQUE OF ROENTGEN EXAMINATION

Previous writers have expressed fear as to the effects of the oral administration of barium in these infants.<sup>2, 3</sup> It has been stated that barium might impact in the pylorus, completing the obstruction, or that barium might be aspirated into the lungs. In our experience the procedure has been found to be entirely harmless.

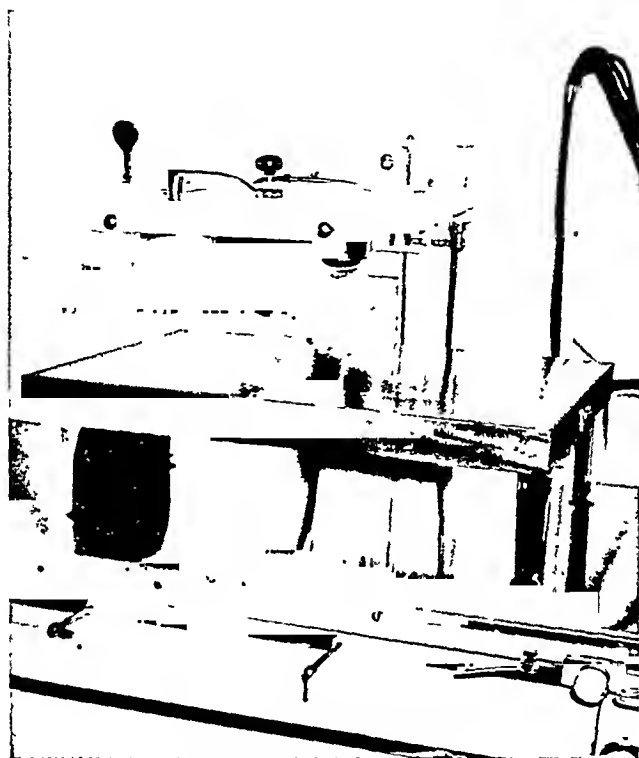


Fig. 7.—Collapsible elevating board utilized in fluoroscopy of infants.

The use of a stomach tube has simplified the examination considerably. After withholding food for a few hours, a sterile gavage tube is inserted into the stomach under fluoroscopic control. Structural changes in the esophagus may be detected by difficulty in the passage of the tube. Any retained fluid and air are aspiration from the stomach and approximately 1 to 2 ounces of a thin barium mixture is instilled. After the completion of the examination residual barium may be withdrawn. It is very important to examine the infant in the oblique and lateral positions in order to visualize properly the pyloric channel. Spot films taken during fluoroscopic examination are used extensively to record fluoroscopic impressions. In our studies we thought it advisable to use a collapsible 7-inch elevating board, placed on the x-ray table top (Fig. 7). The increased tube-to-patient distance serves two purposes. The sharpness of the image of spot roentgenograms is improved, and at the same time the radiation exposure of the patient is reduced.

## RESULTS

*A. Preoperative Studies.*—The results of our findings in patients examined during the manifest stage of the disease are recorded in Table I. In nineteen out of twenty-two cases positive roentgen evidence was obtained. All these cases were proved by operation except for one which was treated medically. In the total of nineteen positive cases, all showed the "string sign" and seven showed, as an additional finding, an indentation of the base of the duodenal cap.

TABLE I. X-RAY STUDIES DURING MANIFEST STAGE OF DISEASE

NO.	NAME	RACE	SEX	SURGICAL PROOF	PALPABLE MASS	X-RAY SIGNS	
						STRING SIGN	INDENTA- TION OF CAP
1	P. C.	W	F	+	0	+	0
2	C. S.	W	M	+	0	+	0
3	P. R.	W	M	+	+	+	0
4	H. G.	W	M	+	+	+	0
5	J. M.	W	F	+	0	+	+
6	J. B.	W	M	+	0	+	0
7	J. J.	W	M	+	+	+	+
8	B. B.	W	M	+	+	0	0
9	McK.	W	M	+	+	+	0
10	L.	W	M	Not oper- ated on	+	+	+
11	L.	W	M	+	+	+	0
12	M. C.	N	F	+	+	+	0
13	W. P.	N	F	+	0	+	+
14	C. M.	N	F	+	0	+	0
15	J. C.	N	M	+	0	+	0
16	J. M.	N	M	+	0	+	+
17	F. S.	N	M	+	0	0	0
18	W. B.	N	M	+	+	0	0
19	E. S.	N	M	+	0	+	+
20	E. W.	N	M	+	+	+	0
21	W. H.	N	M	+	+	+	0
22	R. M.	N	M	+	0	+	+

In the remaining three cases the severity of the obstruction prevented filling of the narrowed pyloric channel, so that a specific diagnosis could not be made (Fig. 1). It is conceivable that administration of antispasmodics might have facilitated visualization of the involved gastric segment.

With proper attention to the pathognomonic features of infantile hypertrophic stenosis, the radiologist may improve his accuracy. During the past five years our radiological service has studied more thoroughly the characteristic features of this disease and has demonstrated the specific radiologic signs with increasing frequency. Concurrently the clinicians have placed greater confidence in roentgen diagnosis and have referred practically all suspected cases for study.

An interesting sidelight of our small series of twenty unselected cases at Grady Memorial Hospital in the past four years is the high incidence of the disease in the Negro race (eleven Negro, nine white). Many earlier reports on this subject stress the rarity of this condition in the Negro race.<sup>14</sup> Our observations tend to confirm the findings of McGahee,<sup>15</sup> who noted that infantile hypertrophic stenosis occurred not infrequently among Negro infants.



*B. Follow-up Studies.*—In sixteen cases follow-up gastrointestinal examinations were performed at intervals of from five months to twenty-two years following successful treatment by operation. The findings of these studies are summarized in Table II. In all but one case (No. 8, aged 1½ years) persistent changes in the most distal portion of the stomach were observed, consisting of varying degrees of narrowing as well as diminished or absent peristalsis (Figs. 8, 9, 10, 11). Several of these patients demonstrated basilar indentation of the duodenal cap. Similar findings were observed in one patient treated medically when examined five months after clinical recovery. We were impressed that despite the radiologic changes proper gastric emptying was a regular occurrence in all these cases. Similar studies were previously undertaken by Runstrom<sup>16</sup> and also Andresen,<sup>13</sup> who noted that a pyloric deformity may persist for many



Fig. 8.



Fig. 9.

Fig. 8.—Hypertrophic pyloric stenosis five months following Fredet-Ramstedt procedure. Note marked narrowing of pyloric channel and indentation of duodenal cap.

Fig. 9.—Case 5, four years following surgery. Note residual distortion of pyloric channel with reappearance of mucosal folds.

TABLE II. FOLLOW-UP FINDINGS

NO.	NAME	RACE	SEX	LENGTH OF FOLLOW-UP INTERVAL	POSITIVE FINDINGS
1	I. H.	W	M	22 years	+
2	V. M.	W	M	13 years	+
3	C.	W	M	10 years	+
4	D. C.	W	M	6 years	+
5	W. P.	N	F	4 years	+
6	W. B.	N	M	3½ years	+
7	P. C.	W	F	2½ years	+
8	F. S.	N	M	16 months	0
9	H. G.	W	M	13 months	+
10	C. S.	W	M	10 months	+
11	P. R.	W	M	10 months	+
12	E. S.	N	M	7 months	+
13	E. St.	W	M	6 months	+
14	C. M.	N	F	6 months	+
15	E. W.	N	M	5 months	+
16	W. H.	N	M	5 months	+



Fig 10—Case 3, ten years following operation Residual narrowing of pyloric segment.



Fig. 11—Case 1, twenty-two years after successful surgical treatment.

years. These radiologic observations suggest that there are, following operative procedures, residual changes in tone or structure at the site of the hypertrophic pyloric stenosis.

These residual changes are of importance to the roentgenologist who occasionally encounters adolescent or adult patients with narrowing or stiffening of the prepyloric or pyloric portion of the stomach. Conceivably, some of these patients may have had hypertrophic pyloric stenosis in infancy.

#### SUMMARY AND CONCLUSIONS

The roentgen criteria of infantile hypertrophic pyloric stenosis are briefly enumerated and a technique of radiologic examination is described.

Roentgen observations of an unselected series of cases in the active stage of infantile hypertrophic pyloric stenosis revealed positive signs in nineteen out of twenty-two cases. These changes consisted of (a) narrowing and stiffening of the stenotic canal in the pyloric tumor ("string sign," "pyloric beak") and (b) indentation of the base of the duodenal cap. These specific signs occur in association with other nonspecific signs such as delayed emptying, gastric hyperperistalsis, and dilatation.

In fifteen out of sixteen cases examined after complete recovery following a Fredet-Ramstedt operation, residual pyloric deformity was observed consisting of varying degrees of narrowing and diminished or absent peristalsis. Generally the postoperative x-ray changes were less pronounced than those seen during the manifest stage of the disease. In one patient distortion of the pyloric segment of the stomach was still present twenty-two years following operation. In spite of these radiologic changes, gastric emptying was entirely normal.

Though in the majority of cases of infantile hypertrophic stenosis the diagnosis may be established on the basis of the clinical studies, there remain many cases in which x-ray examination will materially assist in the establishment of a correct diagnosis.

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## PRECOCIOUS PUBERTY

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THE cases presented herewith emphasize what has been expressed by several others, and particularly stressed by Novak, that, except for the relatively rare instance, precocious puberty in the female is just what the name would imply, i.e., the development of pubertal changes at an earlier time than usual, these changes being based upon the same physiologic processes in the various endocrine glands as are at work during puberty which occurs at the usual time.

In the past the belief has been rather general that when evidences of sexual maturity occurred in girls at an early age, certainly below the age of 8 years, such changes were caused by a tumor of one of the endocrine glands, notably a granulosa cell tumor of the ovary. Thus Crossen<sup>1</sup> states, "for genuine menstruation to take place, there must be considerable development of the genital organs, and this very rarely occurs before the age of ten, except in a patient with granulosa cell tumor."

In virtually all of the textbooks the discussion of precocious puberty begins with a description of pathologic conditions, usually neoplastic, which may exist in one or another of the various endocrine glands, or pathology involving certain portions of the brain, particularly the hypothalamus and floor of the third ventricle, which results in premature changes in the sexual and secondary sexual characteristics of the individual. Reference to those cases of premature sexual development which occur in the absence of any demonstrable pathology, either in the endocrine system or elsewhere, is usually relegated to a short paragraph at the end of the chapter, if mentioned at all.

It is not the purpose of this paper to discuss in any detail the pathologic processes which may occur in the endocrine system, or lesions involving the brain which give rise to premature sexual development changes as part of their manifestations. These have been exhaustively treated within the limits of our present knowledge in other sources. However, a few observations are pertinent.

Almost without exception, in cases of premature sexual development dependent upon pathology involving the endocrine system, such as benign or malignant tumors of the pineal gland or the adrenals or lesions involving portions of the brain, particularly the region of the hypothalamus, other systems are involved, sometimes widely and markedly. This is far from consistent with the evident normality of the pubertal changes which occur in the type of case under discussion. Thus tumors involving the pineal gland cause isosexual changes, but they are almost exclusive in the male. Neoplasms of the adrenals are almost invariably masculinizing in the female, marked by hypertrophy of the clitoris and hirsutism especially, and pathology of the hypophysis and regions of the

<sup>1</sup>Presented in part before the Sixteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Denver, Colo., Sept. 23, 1948.

brain mentioned above involve manifestations of which the sexual or secondary sexual are only a part.

According to Novak,<sup>2</sup> there is no recorded instance of a tumor of the pituitary being the cause of precocious pubertal changes. This is remarkable, considering the fundamental position held by the pituitary in female sexual maturity, and its maintainance after the menarche. Novak also states that of 60,000 gynecologic admissions to the Johns Hopkins Hospital over a period of sixty years, only one case of granulosa cell tumor of the ovary as a cause of precocious puberty was recorded.

In the type of case represented by the four histories which appear below, no pathology, neoplastic or other, was found at the time the patient was first seen, or after, to account for the early onset of pubertal changes. These changes were entirely normal except for the time at which they appeared. The progress of these changes after their appearance was also entirely normal. Novak and others have called cases such as these "precocious puberty of constitutional type." I am in agreement with Novak that cases falling into this class are in the great majority rather than the minority, as it has been the tendency to believe.

In this type, the bone changes also are consistent with normal puberty. Most of these little girls are, from a general standpoint, more mature than others of the same chronological age. In my experience their mental development is advanced. This last is at variance with other recorded observations regarding the mental development of these patients. Thus Novak<sup>3</sup> has previously stated that "the mental development of the patient has been described as very defective, almost all authors speaking of the childish type of mind seen in these patients. For example, Lenz's patient still played with dolls and very small children at the age of 10 years." Of the four patients in my own experience, one was developed at least to her chronological age, and the other three were definitely beyond in comprehension, use of words, personality traits, etc.

Stimulation of bone growth which is normal for puberty is also found in these cases, except that epiphyseal closure is accelerated. Consequently, in the cases which I have observed these little girls were developed beyond their chronological age when first seen and for a time after, but they are all destined to be below the average in height because of early epiphyseal closure.

Novak, in an excellent article which appeared in the January, 1944, issue of the *American Journal of Obstetrics and Gynecology*, cites nine cases of precocious puberty, all of which fell into the group under discussion. Laparotomy was done in six cases, and in none was any neoplastic disease of the ovaries found. In three of these corpora lutea were found, further attesting to the normality of the pubertal changes which had been previously noted. In all cases ovarian enlargement, when found, was due to simple cysts of various kinds. In the four cases presented below, laparotomy was done in two. In one case a definite enlargement of the ovary was found preoperatively, which proved to be a lutein cyst, and multiple small follicle cysts were found in the other. In neither was there any evidence of neoplasm in the ovaries or elsewhere.

In theorizing upon the factor or factors which set in motion sexual maturity at an abnormally early age, the presence of certain genic factors in the chromo-

somes of a recessive character has been postulated,<sup>2, 4</sup> which factors act in conjunction with the endocrine system to "pull the trigger" as Novak puts it, at a time earlier than usual, the changes themselves being within normal limits of puberty. At least in the light of our present knowledge such a postulation seems reasonable.

If one were precise in the use of words, no other designation than precocious puberty would be needed for these cases since the name means nothing except puberty occurring earlier than its usual time. In the various pathologic conditions causing certain changes in the genitalia and secondary sexual characteristics, the diagnosis ought to be simply that of the pathologic process present, recognizing the sexual changes merely as one manifestation of the whole picture. To do otherwise, as we are wont to do with precocious puberty, is equal to having our main interest and attention centered upon the bronzing of the skin in Addison's disease.

An insufficient number of these cases of precocious puberty have been followed for a long enough time to know what happens to all or most of them later, such as the age of their menopause or their fertility. If one accepts the fundamentally physiologic nature of these patients, there is no reason to suppose that they would be different from other women in these respects. Novak<sup>2</sup> recites a case reported by Haller, in which menstruation began at  $2\frac{1}{2}$  years, with the menopause at the age of 52. A patient reported by Robbelen was still menstruating at the age of  $32\frac{1}{2}$  years. The normality of the sexual maturity process in several of these little girls has been further attested by pregnancies which have occurred at an early age.

These patients should be expertly examined, preferably under anesthesia. It is my opinion that laparotomy is not indicated unless palpable evidence is found to indicate it. One is impressed in these cases by the orderliness of normality of the sexual development and the usual absence of evidences of pathology in the pelvis or elsewhere. In the absence of diagnosable pathology, the treatment of these patients consists in psychotherapy—some of it for the patient, but most of it for the mother and the family.

CASE 1.—B. F. was first seen at the age of  $4\frac{1}{2}$  years. Breast development had been noticed at the age of 4 years. There had been no bleeding. The patient appeared beyond her years in general physical and personality development. The breasts were markedly developed. There was a thick, fine down over the pubes and labia, but no axillary hair, and the clitoris was not hypertrophied. General physical examination was negative. Numerous examinations of the pelvis were made, two under anesthesia. No palpable pathology was ever found. Operation was not done. The patient is now 10 years of age, and she has been menstruating regularly and normally since the age of 7 years. The epiphyses at the age of 9 years were practically closed. Her present height is 5 feet.

CASE 2.—N. J. was first seen at the age of 7 years. Enlargement of the breasts had begun at the age of 5 years, and had been progressive. Physical and mental development appeared beyond her chronological age. The breasts were well developed, with large, pigmented areolae. There was a considerable amount of long, black, pubic hair. There was no axillary hair. The genitalia had the characteristics of late puberty. Pelvic examination was made several

times, once under anesthesia. There was never any palpable pathology. The first menstrual period occurred at the age of 7 years, and has been regular and normal since. She is now 9 years of age.



Fig. 1.

Fig. 1.—Case 1. Photograph at age of  $8\frac{1}{2}$  years. Breast development began at 4 years. Menstruation began at 7 years.

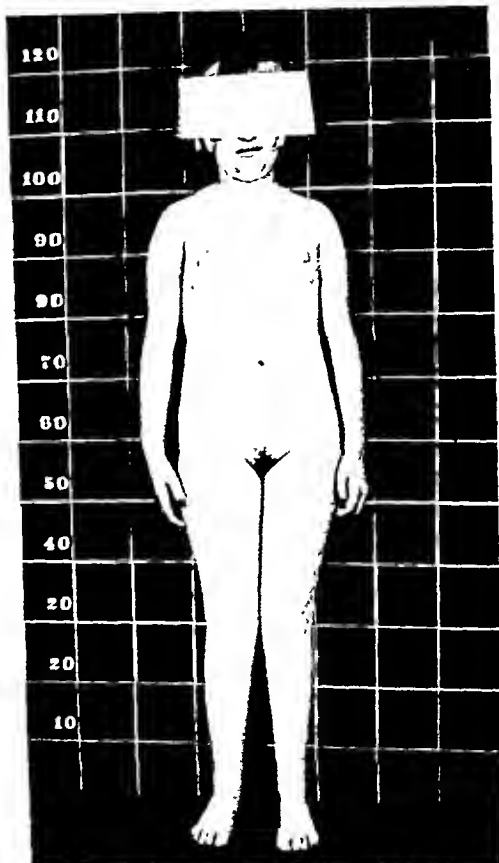


Fig. 2.

Fig. 2.—Case 2. Photograph at age of 7 years. Breast development began at 5 years. Menstruation began at 7 years.

CASE 3.—E. B. was first seen at the age of 8 years. Her breasts were markedly developed before the age of 6 years. Menstruation had begun at  $7\frac{1}{2}$  years, and had been fairly regular and otherwise normal since onset. Physical and mental development appeared beyond her chronological age. Examination revealed a girl who might have been 14 years old. The genitalia were adult in appearance. There was a dense growth of pubic and axillary hair. Pelvic examination disclosed a mass in the right lower pelvis which seemed to be an ovary about 6 cm. in diameter. The uterocervical ratio was roughly 2:1.

Laparotomy was done, and the right ovary removed. The enlargement proved to be a lutein cyst, with many normal follicles in various stages of maturity.



somes of a recessive character has been postulated,<sup>2, 4</sup> which factors act in conjunction with the endocrine system to "pull the trigger" as Novak puts it, at a time earlier than usual, the changes themselves being within normal limits of puberty. At least in the light of our present knowledge such a postulation seems reasonable.

If one were precise in the use of words, no other designation than precocious puberty would be needed for these cases since the name means nothing except puberty occurring earlier than its usual time. In the various pathologic conditions causing certain changes in the genitalia and secondary sexual characteristics, the diagnosis ought to be simply that of the pathologic process present, recognizing the sexual changes merely as one manifestation of the whole picture. To do otherwise, as we are wont to do with precocious puberty, is equal to having our main interest and attention centered upon the bronzing of the skin in Addison's disease.

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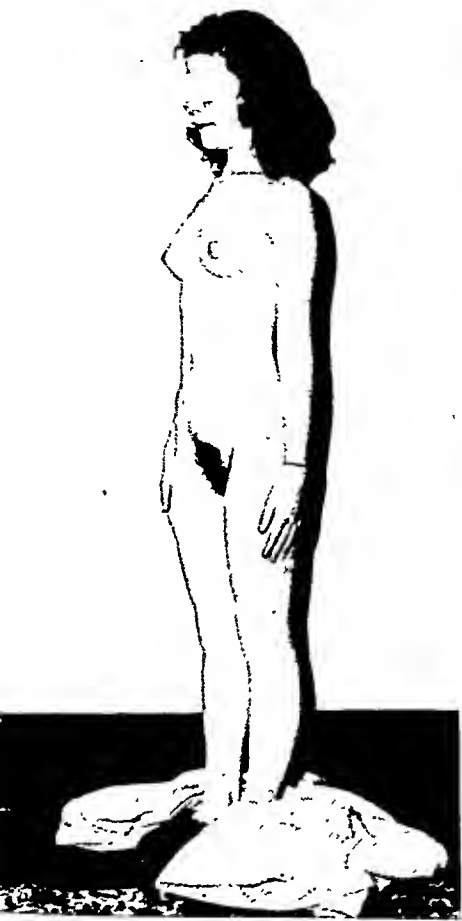


Fig. 1.

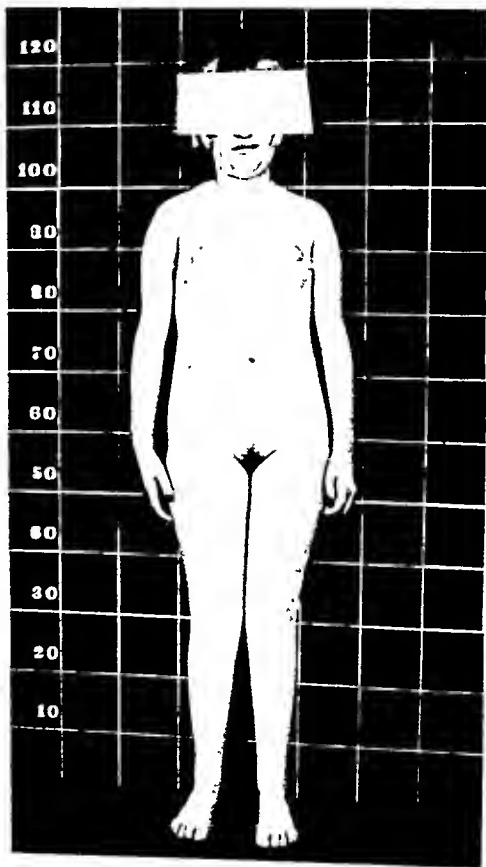


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Laparotomy was done, and the right ovary removed. The enlargement proved to be a lutein cyst, with many normal follicles in various stages of maturity.

There has been no regression in any of the patient's adult characteristics since the operation, and menstruation has occurred regularly and normally since.

X-ray studies were made in all of the above cases. No intracranial pathology was found. Advancement of the bone age was found in all cases, as shown in the accompanying illustrations.

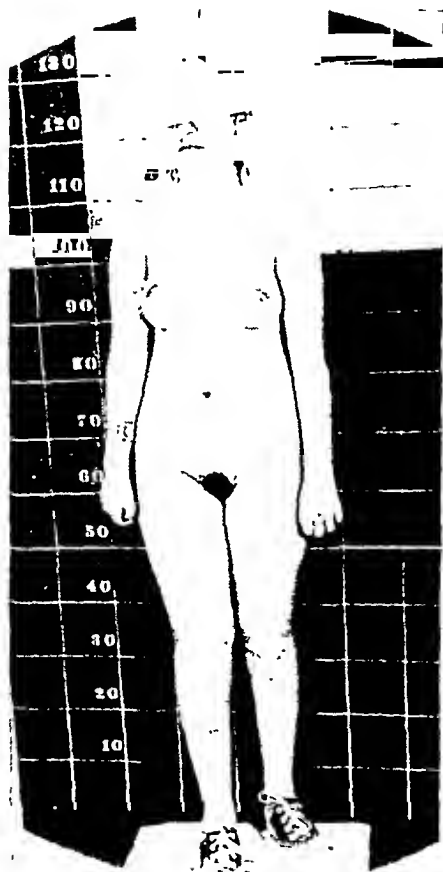


Fig. 3.—Case 3. Photograph at age of 8 years. Breast development began at 5 years. Menstruation began at  $7\frac{1}{2}$  years.

CASE 4.—E. M. Patient was admitted to Children's Hospital in Denver in 1942, at the age of 4 years. She had gained from 35 to 57 pounds during the previous year. During the four months previous to her admission to the hospital, she had been nervous and irritable, which was ascribed to the rather large amounts of thyroid which she had been receiving. Breast enlargement had been noticed at the age of  $3\frac{1}{2}$  years. There had been no bleeding. Examination revealed a girl somewhat average height for her age, and overweight. The breasts were moderately enlarged. Areolae were distinct. There was moderate enlargement of the genitalia but the clitoris was not hypertrophied. There was no pubic or axillary hair. Vaginal smears showed squamous cells which were of the adult vaginal type. Roentgenograms were made at this time of the skull and upper extremities. The sella tureica was normal. Examination of the wrists showed advancement of the bone age, there being seven of the eight carpal

bones present (normal for age 4 or 5). There was considerable development of the radial epiphyses in advance of that considered normal.

Exploratory laparotomy was done for possible granulosa cell tumor of the ovary as a cause of the precocious sexual development. The ovaries were about 2 by 1 cm. in size and contained multiple cysts. Section of the left ovary was removed for pathologic examination. Kidney regions were palpated and no abnormalities were found.

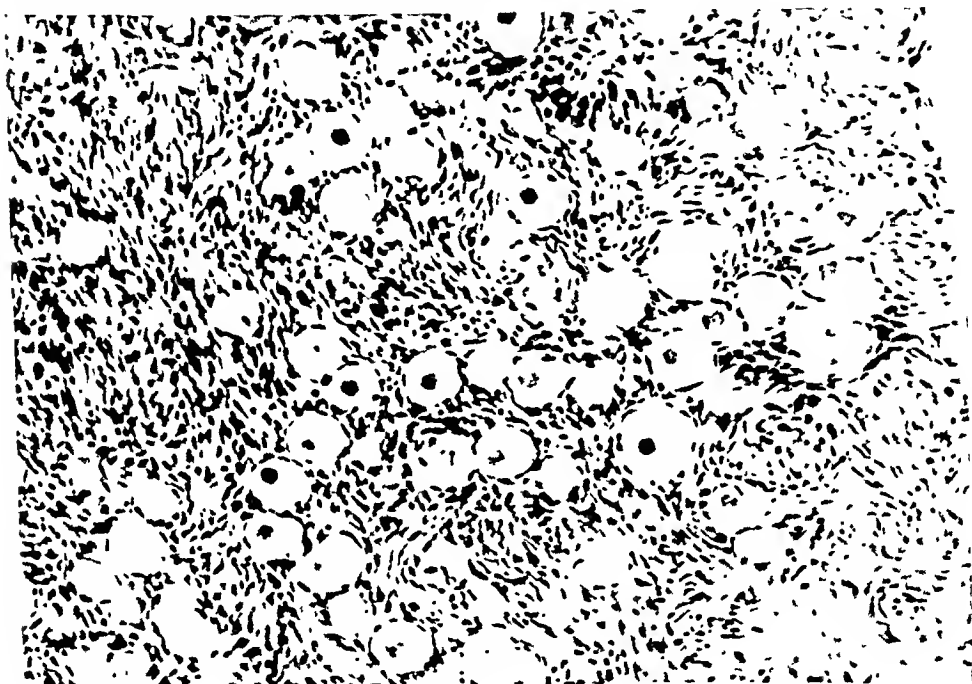


Fig. 4.—Case 4. Sections of ovary removed at age of 4½ years, showing normal follicles.

*Microscopic Examination.*—"The sections include the cortex and a portion of the medulla of the ovary. The cortex shows normal anatomical relationships and contains many primordial follicles. Several portions of follicle cysts are included in the sections. These are of the atretic follicle type, with a prominent theca interna layer. One of them contains fresh hemorrhage. Diagnosis: Follicle cysts of immature ovary."

This patient is of particular interest because she has been followed subsequently by her pediatrician, Dr. John M. Nelson, and also by the Child Research Council of the University of Colorado Medical Center. She is now 11 years of age. She began to menstruate at the age of 6, and her periods have been regular and normal to date.

The following examinations and reports were made by the Child Research Council when the patient was 9½ years of age:

*X-ray Study.*—"The bone to bone proportions are all well within average limits and present no peculiar relationships. Lengths are average except for lower leg bones which are somewhat above average for her age. Total body height (4 feet 8 inches) is similarly somewhat above average for her age. The disturbing element in this picture is the maturity of the skeleton. Many of the centers have already fused to shafts, especially at the elbow and ankle.

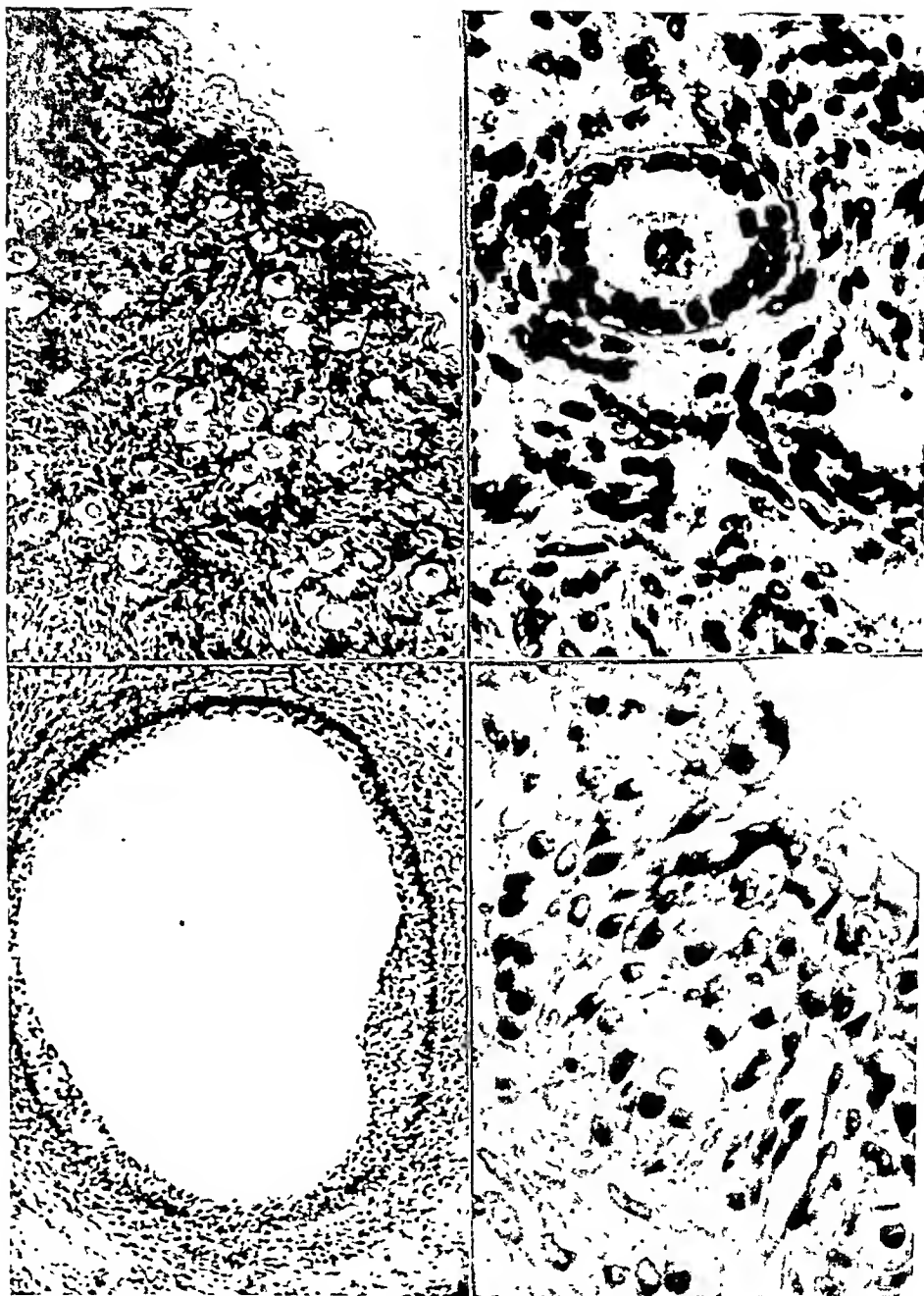


Fig. 5.—Case 3. Sections from right ovary: upper left, primordial follicles; upper right, follicle in early stage of development; lower left, fully developed follicle; lower right, lining membrane of the cyst.



Fig. 6.



Fig. 7.

Fig. 6.—Normal bone development in a girl of 9 years. Immature. Epiphyses open.  
 Fig. 7.—Case 1. Taken at age 9 years, showing advanced bone age.

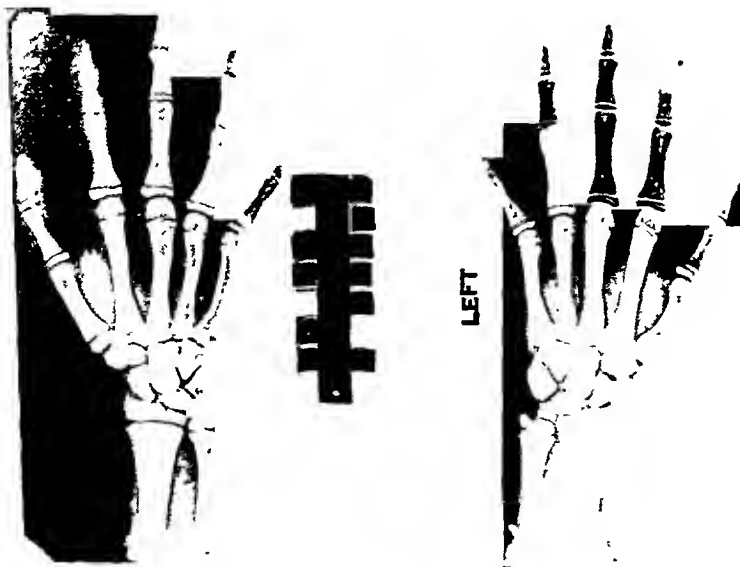


Fig. 8.—Case 2. Taken at age 7 years, showing advanced bone age.

The knee, shoulder, and hip epiphyses are almost fused and will probably close within 6 months. Thus the patient is at least four or five years accelerated over other girls her age. She cannot be expected to gain more than a possible inch in height from long bone growth. She may gain another two inches from the spine, but she is certainly destined to be a very short adult, probably under 5 feet. The skull pictures show a sella of normal size with normal density of the clinoids and floor.

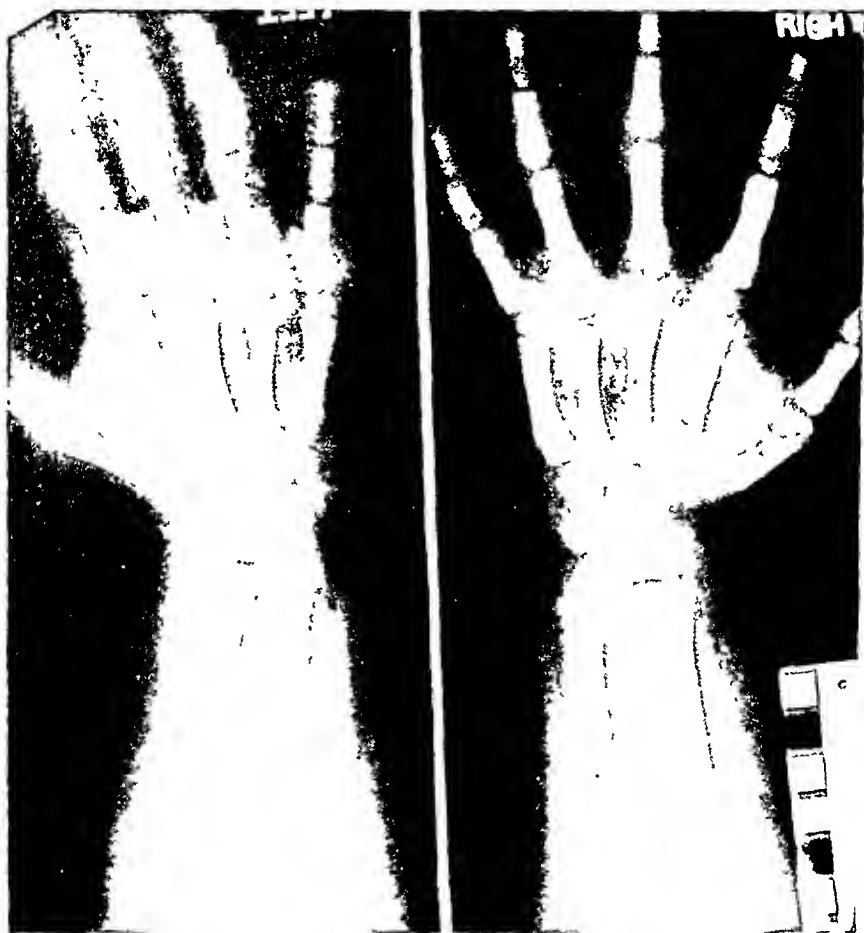


Fig. 9—Case 4. Taken at age  $1\frac{1}{2}$  years, showing advanced bone age

"It would be interesting to know the time at which fusion of the epiphyses began. Usually one expects to see fusion of the capitellum to the humeral shaft shortly before the menarche. In this case, the patient's growth suggests that fusion has occurred more recently, probably within the past year." (Marion Maresh, M.D.)

*Report From Psychiatrist.*—"Patient has an I.Q. of 127. She appears to be functioning at a very superior level for her age and to have a mental age over two and one-half years above her chronological age. Vocabulary was on

the 14-year level. Reasoning, comprehension, and ability to express herself were all superior." (Cotter Hirshberg, M.D.)

Basal metabolic rate at this time was minus 10 per cent.



Fig. 10.—Also Case 4. Taken at age 9½ years, showing almost complete maturity of bones.

#### CONCLUSIONS

1. Except rarely, precocious puberty in the female appears to be what the name implies, viz., the onset and development of sexual maturity which is physiologic except for the time at which it begins.

2. This maturity involves not only the genitalia and secondary sex characteristics but the skeletal system as well. Because of the early closure of the epiphyses, these individuals are usually of short stature.

3. These patients should be expertly examined and a pelvic examination should be done under anesthesia. Surgery is not indicated unless palpable evidence is found to justify it.

4. Granulosa cell tumor of the ovary is rare as a cause of premature sexual development. Tumors of other endocrine glands, when accompanied by sexual change, are heterosexual in their manifestations. Lesions of certain brain areas, when accompanied by sexual changes, are also accompanied by other system changes which, in most cases, exceed those of the genitalia or secondary sex characteristics.

5. Treatment consists in psychotherapy directed to the patient, but particularly to the mother or family during the years which lie between the appear-



ance of sexual maturation and the time when these self-conscious little girls will merge with the group in their physical appearance, or, more correctly, when the group merges with them. .

I wish to express my thanks to Dr. F. Craig Johnson of Denver, through whom Cases 2 and 3 were referred.

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## A METHOD OF DETERMINATION OF SERUM pH APPLICABLE FOR CLINICAL USE

W. M. KELSEY, M.D., AND L. B. LEINBACH, B.S.  
WINSTON-SALEM, N. C.

DETERMINATION of the serum pH is of importance to the clinician since the carbon-dioxide combining power does not give accurate information concerning the acid-base balance in salicylate intoxication or in diseases associated with disturbances of respiration. Frequently it is difficult to decide from clinical and chemical evidence whether the patient is alkalotic or acidotic. In such a situation errors of pH 0.05 would be of no significance. A method which would fall within this range of error and would be applicable for clinical use would be of value. Methods of determining the serum or blood pH have not been of general clinical value because of technique required.<sup>1</sup> A trained technician, such as is not available in the average hospital, is necessary if precise results are to be obtained. If the determination is to be run at the bedside it is necessary to have the equipment and the technician available at all times. If the blood is to be sealed by the most exact methods, equipment is required which is not readily available and is expensive.

These studies were carried out because no data could be found in the literature concerning the effect of various factors on the serum pH determination when the blood was drawn under mineral oil. Since minor variations of pH do not invalidate its use in clinical medicine it was felt valuable to find out how long the blood could remain under oil and be centrifuged without significantly altering the determination. The technical errors inherent in this method are well understood, and it was surprising that the determinations were as constant as they turned out to be.

### METHOD

A standard Beckman pH meter was used. The electrodes were 2.5 inch sealed glass and calomel electrodes. The open type electrode was used. Seven milliliter specimen vials were used for collection of the blood. Tight fitting tuberculin syringes with short beveled 22-gauge needles were found convenient for withdrawing the serum. Ordinary heavy mineral oil was used.

Blood was drawn under mineral oil in tight-fitting, dry syringes with precautions against the introduction of air into the syringe. Depending upon the hematocrit, 2 to 3 c.c. of blood were necessary. The sample was placed under 4 to 6 mm. of mineral oil in the vials and was centrifuged for five minutes at 2,500 r.p.m. After the pH meter was standardized, the serum was drawn into the tuberculin syringe slowly to prevent the introduction of air. Oil was cleaned from the needle, and the serum was introduced slowly into the cup with the tip of the needle against the bottom of the cup to prevent excessive contact

<sup>1</sup>From the Department of Pediatrics of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem 7, N. C.

with air. The determination was run immediately. Certain precautions had to be taken. The glassware had to be clean and dry. If the electrodes touched either the sides of the cup or each other the results were variable. The standardization of the meter and the determinations were carried out according to directions accompanying the instrument.

### RESULTS

Studies were done to determine the effect of various factors on the determination. Blood was allowed to remain under oil for varying lengths of time in order to find out how long the sample may be held before the determination is made. (Table I.) The sample was centrifuged for varying lengths of time to see if there was a significant change with moderate variations in centrifugation. (Table II.) Determinations were made comparing results obtained with a sealed electrode and open type of electrode. (Table III.) Multiple determinations were made on twenty-five samples using the open electrode. (Table IV.) The maximum error in the split samples was pH 0.07. The average variation was plus or minus pH 0.03. These figures show that for the accuracy desired the blood may remain under oil for three hours and may be centrifuged for ten minutes without effecting the determination significantly. Values obtained with the use of sealed and open electrodes are so similar that the trouble of using the sealed electrode is not worth while. Since the determina-

TABLE I. VARIATIONS OF PH IN SAMPLES REMAINING UNDER OIL VARYING LENGTHS OF TIME

MINUTES					
15	60	120	240	360	
7.5	7.48	7.5	7.58	7.6	
7.36	7.42	7.42	7.46	7.52	
7.42	7.45	7.44	7.48	7.48	
7.48	7.44	7.5	7.52	7.57	
7.22	7.25	7.3	7.36	7.37	
7.51	7.56	7.55	7.6	7.58	
7.49	7.43	7.5	7.51	7.57	
7.32	7.32	7.38	7.4	7.42	
7.58	7.5	7.53	7.56	7.7	
7.53	7.51	7.55	7.56	7.6	

TABLE II. VARIATIONS OF PH IN SAMPLES CENTRIFUGED VARYING LENGTHS OF TIME

MINUTES CENTRI- FUGED	SAMPLE									
	1	2	3	4	5	6	7	8	9	10
5	0	7.36	7.46	7.4	7.22	7.42	7.5	7.44	7.5	7.1
10	7.35	7.41	7.5	7.4	7.25	7.4	7.48	7.44	7.52	7.08
20	7.45	7.48	7.52	7.44	7.3	7.44	7.52	7.51	7.56	7.16

TABLE III. VARIATIONS OF PH WITH SEALED AND OPEN ELECTRODES

ELECTRODE	SAMPLE									
	1	2	3	4	5	6	7	8	9	10
Open electrode	7.32	7.45	7.41	7.48	7.48	7.42	7.48	7.22	7.08	7.45
Sealed electrode	7.35	7.45	7.35	7.48	7.48	7.46	7.5	7.2	7.13	7.4

TABLE IV. VARIATIONS OF pH IN SINGLE SAMPLES

7.52	7.5	7.46	7.5	7.45	7.5	7.48	7.52	7.64
7.5	7.52	7.42	7.46	7.4	7.48	7.48	7.52	7.61
7.45	7.5							
7.68	7.59	7.72	7.74	7.64	7.14	7.32	7.81	
7.68	7.58	7.69	7.72	7.61	7.1	7.3	7.79	
7.72	7.74	7.44	7.46	7.22	7.13	7.51	7.33	
7.68	7.72	7.42	7.42	7.2	7.08	7.5	7.51	

tion can be made several hours after the sample is drawn, the method is valuable because the sample can be obtained at the time the patient is admitted and can be run when the technician is available. No references could be found which indicated the variations which would be expected when the collection was made in the manner described.

## pH DETERMINATIONS IN NORMAL PATIENTS

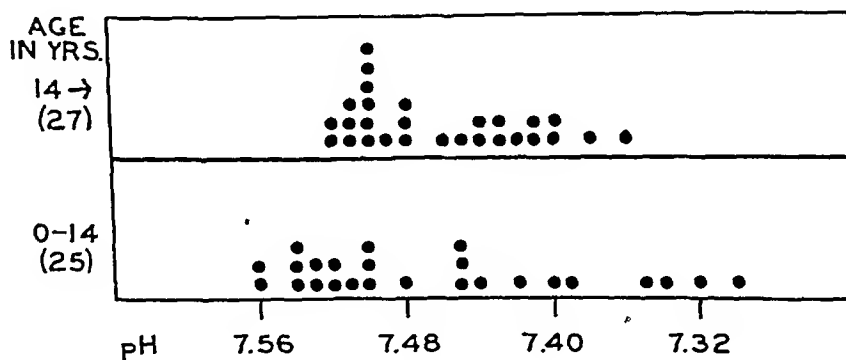


Fig. 1.

Normal values were obtained from people who had no disease process known to produce abnormalities in acid-base balance. (Fig. 1.) These values, which varied from 7.3 through 7.56, were slightly higher than the range of pH 7.33 through 7.51 which were accepted as normal by Earle and Cullen.<sup>2</sup> The slightly high values obtained were probably a result of the errors inherent in the method. A great majority of the determinations were done by a technician who had no previous training in handling biological materials.

### COMMENTS

This method is not intended for exact determinations of the serum pH. Carbon dioxide is soluble in mineral oil. Therefore, the time the blood remains under oil and the speed and time of centrifugation should effect the diffusion of carbon dioxide. Glycolysis should alter the pH. However, empiric observations indicate that these factors do not alter the pH within the limits desired. Interfacial tension probably prevents the diffusion of carbon dioxide in spite of its relatively high solubility in mineral oil. Varying amounts of mineral oil did not alter the determinations.

This method has been checked by bedside determinations on whole blood and on heparinized blood. These determinations have checked closely with simultaneous ones done by the method described above. It has also been checked on patients with known alkalosis and acidosis. The determinations in these cases have fallen within limits which were expected from the clinical and laboratory data available.

This simple method for the determination of serum pH is applicable for use in a clinical laboratory. This method has proved to be practical since blood may be obtained at the time the studies are required and the blood can then be held until the technician can be called. It does not demand that the technician be present at all times, and does not require special preparation of equipment before the blood is obtained. A technician who has had average training can get consistent results. This method cannot be used for purposes such as in the calculation of the carbon-dioxide tension where determinations of accuracy greater than pH 0.05 is required, but is of great aid in differentiating alkalosis from acidosis and in indicating the degree of decompensation of the acid-base balance.

The sample can remain under oil for three hours and may be centrifuged for ten minutes without significantly altering the determination.

#### SUMMARY

A method for the determination of serum pH which is applicable for use in a clinical laboratory is described.

The effects of various factors on serum pH determinations are described.

Normal values obtained by this method are given.

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# EFFECT OF TERMINAL DISINFECTION AND OTHER FACTORS ON THE STABILITY OF ASCORBIC ACID IN RELIQUEFIED MILK PRODUCTS USED IN INFANT FEEDING

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COLUMBUS, OHIO

THE terminal disinfection of milk formulas for infant feeding has been suggested as a standard procedure for hospital formula rooms. It seems advisable that any adopted technique be based upon a time-temperature treatment that will effect the necessary microbial and toxin inactivation with a minimum loss of factors important in the nutrition of the infant. Ascorbic acid (vitamin C) is one of these factors that is readily destroyed by oxidation. Although the vitamin, when in aqueous solution, is stable to heat if oxidizing substances including dissolved oxygen are absent, heating accelerates the oxidation when oxidizing substances are present. The purpose of this investigation, therefore, was to study the effect of various temperature treatments and certain other influencing factors upon the stability of ascorbic acid in formulas for infant feeding made from fortified milk powders.

The literature pertaining to the stability of ascorbic acid in milk, to the effect of processing treatments, and to the oxidative catalysts is extensive. Most of the investigational work, however, has dealt primarily with the stability of the naturally occurring vitamin. The few available data concerning milk products fortified with synthetic ascorbic acid have been collected from studies of fluid market milk or evaporated milk. Although such information may not be directly applicable to the stability of the vitamin in a reliquefied powdered milk product, a brief review of the literature on this limited phase of the subject is presented.

Woessner, Weekel, and Schuette<sup>1</sup> showed that pasteurizing unfortified and fortified fluid milk at 145° to 150° F. for thirty minutes caused an approximate 20 per cent loss of total ascorbic acid. Their data show that the destruction of ascorbic acid appears to be more dependent on the time the milk is held at an elevated temperature than on the temperature itself. They conclude that vitamin C fortification of fluid milk is practical if contamination with copper is rigidly prevented and the milk is protected from light.

Calculations from data presented by Hartman<sup>2</sup> showed that freshly pasteurized mixed herd milk lost 16 per cent of its natural reduced ascorbic acid during the first forty-eight hours of storage at approximately 40° F. The rate of loss was 0.06 mg. per liter of milk per hour. Some of the same milk fortified with 25 mg. of synthetic ascorbic acid per liter lost only 10 per cent of its reduced ascorbic acid during the first forty-eight hours of storage. The rate of loss, however, was 0.09 mg. per liter per hour. Some of the same milk intentionally contaminated with 6.4 ppm. copper, but containing no synthetic

<sup>1</sup>From the M and R Dietetic Laboratories, Inc.

ascorbic acid, lost 87 per cent of its reduced ascorbic acid during the first two hours of storage. The rate of loss was 8.5 mg. per liter per hour. The same copper-contaminated milk, to which 25 mg. of synthetic ascorbic per liter was added, lost 62 per cent of its reduced ascorbic acid during the first two hours of storage. The rate of loss, however, was 13.9 mg. per liter per hour.

Holmes and Jones<sup>3</sup> reported that an 11 per cent loss of reduced ascorbic acid per day during the first three days of refrigerator storage occurred in raw cow's milk that had been fortified with ascorbic acid at the rate of 75 mg. per liter. These investigators also observed that milk fortified with 150 mg. of ascorbic acid per liter lost an average of 6 per cent per day under the same conditions. It will be noted that the loss of ascorbic acid in milligrams per hour was a little greater in the case of the higher fortification.

Josephson and Doan<sup>4</sup> concluded from their studies that it is commercially feasible to fortify evaporated milk with ascorbic acid provided the cans are vacuum sealed.

Spray-dried fat-containing milk products are customarily packaged in hermetically sealed containers in inert gas after first being subjected to high vacuum. Such procedure, while originally instituted as a means of inhibiting lipid oxidation, can be anticipated as serving to increase the stability of the ascorbic acid present in dried milk products. Results obtained in our laboratory showed that milk powders packaged in this manner lost only 2.7 per cent of their total ascorbic acid during one year of storage. The product, when packaged, contained 296 mg. of ascorbic acid per pound and one year later contained 288 mg. per pound.

#### EXPERIMENTAL PROCEDURES

The dried milk product\* used in this study was one of the products designed especially for infant feeding. The composition of this product is 13.75 per cent protein, 26.85 per cent fat, 52.90 per cent lactose, 4.50 per cent ash, and 2.0 per cent moisture. All samples used in this study were fortified with synthetic crystalline ascorbic acid, the ascorbic acid being added to the liquid product previous to drying. The batches of powder used were made in regular commercial operation by the spray drying process. The results obtained in this study, consequently, should be fairly representative of the product of commerce. A standard ratio for reliquefying the powder was used throughout the investigation, the ratio being  $\frac{1}{4}$  lb. powder made up to one quart of liquid with warm water.

All formula samples, after having been subjected to the various treatments described herein, were placed in an ordinary household electric refrigerator for storage until analyzed for ascorbic acid content. Since it is common practice, both in the home and in the hospital, to prepare a twenty-four-hour formula feeding requirement at one time and to store the bottles until used, the investigational data herein reported were collected twenty-four hours after reliquefaction of the milk powder, unless otherwise specified. It was felt that such a procedure would allow a more reliable estimation to be made of the minimum amount of ascorbic acid being consumed by the infant in a twenty-four-hour period.

\*Similac.

The analytical procedure used for determining reduced ascorbic acid was a modification of the Mindlin and Butler<sup>5</sup> procedure as described by Woessner, Elvehjem, and Schuette.<sup>6, 7</sup> The Willberg<sup>8</sup> solution as modified by Woessner, Elvehjem, and Schuette<sup>6, 7</sup> was used for producing a clarified serum and to prevent oxidation of the ascorbic acid except that produced by the indophenol reagent. The procedure used for determining the dehydro form of the vitamin was essentially the same as that described by these same investigators.<sup>6, 7</sup>

It will be seen from data presented later in this paper on formula samples subjected to heat that the ascorbic acid content after twenty-four hours appeared to be comparatively quite high. It was thought that perhaps spurious heat-generated reducing substances were reacting with the indophenol reagent to give these high values. A determination for interfering reductones, as these compounds are collectively termed by some workers, according to the method of Robinson and Stotz as given by Rubin, Jahns, and Bauernfeind<sup>9</sup> gave negative results. Josephson and Doan<sup>4</sup> stated that the acid precipitation and filtration procedure which they used removed all interfering nonascorbic acid reducing substances. Since their procedure was quite similar to that used in this investigation, it may be taken as evidence substantiating a claim of the absence of interfering reductones.

*Heat Treatments.*—After reliquefaction, the liquid formulas were transferred to 8-ounce nursing bottles (unless otherwise specified), stoppered, and treated as indicated in the accompanying tables of experimental results. Those treatments designated "A. S. Co." were heat treated in accordance with the procedure for terminal disinfection recommended by the American Sterilizer Co.; the procedure is essentially that used at Children's Hospital\* in Columbus, Ohio. The specific procedure used in these studies consisted in placing the formula bottles in the sterilizer, raising the temperature inside the sterilizer with flowing steam to 180° F. in two minutes and to at least 190° F. within five minutes after heating started, and thereafter allowing the sterilizer temperature to increase slowly toward 210 to 212° F. during the remainder of the heating period. The indicated heating times given with the "A. S. Co." data in Tables II and III designate the period during which the temperature inside the sterilizer was at 180° F., or above. The actual temperature of the formula following such treatment was 180° F. in the case of a seven-minute exposure and 205 to 210° F. for fifteen minutes' exposure.

The heated samples were cooled to about 70° F. in cold water immediately after the indicated heat treatment unless otherwise specified. In order to determine what effect slower cooling has upon ascorbic acid losses, samples were allowed to stand in the laboratory, under ordinary summer temperature conditions, protected from light for three hours after removal from the sterilizer. Since ascorbic acid is known to be photolabile, the effect of three-hour exposures to the diffuse light of the laboratory was determined and compared with the previously described light-protected samples.

\*We wish to thank Dr. Warren Wheeler of Children's Hospital for his interest and kindly cooperation in this study.



*Copper, Iron, Chlorine.*—The effect of copper on ascorbic acid in solution is well established. Somewhat less information is available concerning the effect of iron. Chlorine, being an oxidizing agent, conceivably might affect the stability of ascorbic acid in solution. In order to study the effect of these substances, formulas were made up with waters intentionally contaminated, respectively, with copper (as copper chloride), iron (as ferrous sulfate), and chlorine (as calcium hypochlorite) and the results compared with those obtained on untreated control samples.

*Warming the Refrigerator-Stored Formulas.*—Since it is general practice to warm formulas held in the refrigerator previous to feeding to body temperature, this procedure was followed in some trials and the ascorbic acid content was compared with that of samples not so treated.

*Stability of Ascorbic Acid in Open Cans of the Powder.*—A number of cans of the powder were analyzed for ascorbic acid immediately after opening and periodically thereafter for eight to ten days. The lids were loosely placed on the cans during this period so as to protect the contents from exposure to light.

#### EXPERIMENTAL RESULTS

The average reduced ascorbic content of the freshly opened cans of the dried milk product was 300 mg. per pound and the average total ascorbic acid was 323 mg. per pound. The average losses four days after opening the cans, the top layer being removed daily for analysis (the average length of time a can containing one pound of the dried product remains open before its contents are completely used in feeding an infant is about four days) were 2.8 per cent of the reduced ascorbic acid and 3.2 per cent of the total ascorbic acid. The average losses eight days after opening the cans were 6.3 per cent and 6.7 per cent of the reduced and total ascorbic acid, respectively.

Table I shows the amount of ascorbic acid in one quart of the reliquefied product ( $\frac{1}{4}$  lb. of powder made to one quart of liquid) when freshly made up and after being held twenty-four hours in an electric refrigerator.

TABLE I. ASCORBIC ACID CONTENT OF FRESHLY RELIQUEFIED PRODUCT AND AFTER TWENTY-FOUR HOURS REFRIGERATOR STORAGE

	MG. ASCORBIC ACID PER QUART		PER CENT LOSS	
	REDUCED	TOTAL	REDUCED	TOTAL
Freshly made	71.4	77.2	---	---
24-hour storage	62.8	68.6	12.0	11.1

The effects of various heat treatments, cooling procedures, and exposure to diffused daylight on the ascorbic acid content of reliquefied product are shown by the data in Table II. The values given are the concentrations of ascorbic acid in the formulas immediately after reliquefaction and twenty-four hours after reliquefaction. All samples were held in the electric refrigerator after receiving the treatments indicated in the table until ready for analysis.

A formula contained in stoppered nursing bottles heated at 230° F. (about 7 lb. pressure) for fifteen minutes, cooled in ice water quickly, and analyzed immediately, lost 8.0 per cent and 13.6 per cent of its reduced and total

ascorbic acid, respectively. Nursing bottles containing a formula were heated by immersion in a boiling water bath for fifteen minutes, quickly cooled in ice water, and the formula was analyzed immediately thereafter. The formula

TABLE II. ASCORBIC ACID CONTENT OF VARIOUSLY TREATED PRODUCT FORMULAS IMMEDIATELY AFTER AND TWENTY-FOUR HOURS AFTER RELIQUEFACTION

FORMULA TREATMENT	MG. ASCORBIC ACID PER QUART				% LOSS IN	
	0 HR.		24 HR.		24 HR.	
	REDUCED	TOTAL	REDUCED	TOTAL	REDUCED	TOTAL
1—A. S. Co., 7 min.; cooled quickly.	71.8	76.9	54.8	62.0	23.7	19.4
2—A. S. Co., 7 min.; room temp. 3 hr., protected from light.	71.8	76.9	54.5	58.9	24.1	23.4
3—A. S. Co., 15 min.; cooled quickly.	71.8	76.9	55.2	62.0	23.1	19.4
4—A. S. Co., 15 min.; room temp. 3 hr., protected from light.	71.8	76.9	55.2	59.3	23.1	22.9
5—Heated in water bath, temp. raised from 180° to 200° F. in 10 min.; cooled quickly.	70.6	76.0	56.4	59.7	20.1	21.4
6—Heated as No. 5; room temp. 3 hr., protected from light.	70.3	75.1	53.4	57.2	24.0	23.8
7—Heated as No. 5; room temp. 3 hr., exposed to diffused light.	70.3	75.1	51.7	54.5	26.5	27.4
8—Heated as No. 5; room temp. 18 hr., protected from light.	71.4	78.6	51.7	54.3	27.6	30.9
9—Heated at 230° F. (7 lb. press.) for 5 min.; cooled quickly.	71.4	79.6	64.1	67.7	10.2	14.9
10—Heated as No. 9; room temp. 3 hr., protected from light.	71.4	79.6	64.1	66.2	10.2	16.8
11—Heated at 230° F. (7 lb. press.) 15 min.; cooled quickly.	72.4	77.8	60.2	64.1	16.9	17.6
12—Heated in boiling water bath 15 min.; cooled quickly.	72.4	78.1	56.1	62.0	22.5	20.6

TABLE III. EFFECT OF ADDING COPPER, IRON, AND CHLORINE ON THE STABILITY OF ASCORBIC ACID IN RELIQUEFIED DRY MILK PRODUCT

FORMULA TREATMENT	MG. ASCORBIC ACID PER QUART				% LOSS IN	
	0 HR.		24 HR.		24 HR.	
	REDUCED	TOTAL	REDUCED	TOTAL	REDUCED	TOTAL
1—1 ppm. Cu; not heated.	76.5	84.8	29.0	37.2	62.1	56.1
2—1 ppm. Cu; heated at 190° F. for 5 min.	76.5	84.8	23.8	24.8	69.3	70.8
3—0.5 ppm. Cu; not heated.	77.6	84.8	45.5	47.6	51.4	43.9
4—0.1 ppm. Cu; A. S. Co., 15 min.; room temp. 3 hr. protected from light.	*	77.6	*	61.0	*	21.4
5—0.2 ppm. Cu; otherwise as No. 4	*	77.6	*	57.9	*	25.4
6—0.2 ppm. Cu; not heated.	*	77.6	*	53.8	*	30.7
7—1 ppm. Fe <sup>++</sup> ; A. S. Co., 15 min.; room temp. 3 hr. protected from light.	*	78.6	*	60.0	*	23.7
8—2 ppm. Fe <sup>++</sup> ; otherwise as No. 7.	*	78.6	*	58.9	*	25.1
9—1 ppm. Fe <sup>++</sup> ; not heated.	*	84.8	*	69.3	*	18.3
10—2.5 ppm. Cl added; not heated.	70.8	75.5	66.2	67.7	6.5	10.3
11—5 ppm. Cl added; not heated.	72.4	75.5	63.1	67.2	12.8	11.0
12—10 ppm. Cl added; not heated.	69.3	77.6	57.9	65.2	16.5	16.0
13—10 ppm. Cl added; heated in boiling water bath for 15 min.	69.3	77.6	54.8	55.8	20.9	28.1
14—25 ppm. Cl added; not heated.	67.2	74.5	45.0	52.7	33.0	29.3
15—25 ppm. Cl added; heated at 230° F. (7 lbs. press.) for 15 min.; cooled quickly.	65.2	71.4	43.4	48.6	33.4	31.9

\*Reduced ascorbic acid not determined.

lost 14.7 per cent and 17.3 per cent of its reduced and total ascorbic acid, respectively. The same formula, contained in an open vessel, was heated directly over an open flame, cooled quickly in an ice water bath, and analyzed immediately. The formula lost 6.7 per cent and 9.9 per cent of its reduced and total ascorbic acid, respectively.

The effects of added copper, iron, and chlorine on the ascorbic acid content of the reliquefied product are shown by the data in Table III.

Warming stored samples of the formula to body temperature just prior to analysis caused no decrease in the concentration of ascorbic acid. When such warmed samples were allowed to stand in a boiling water bath for five minutes, or longer, the ascorbic acid concentration was decreased by as much as 15 per cent.

#### DISCUSSION

The loss of ascorbic acid in an opened one-pound can of the dried milk product is negligible at the end of four days, which is the usual length of time a can of the product remains open in the home. The average loss in the reliquefied product (unheated after makeup) during twenty-four hours of refrigerator storage is about the same as that reported by Hohmes and Jones<sup>3</sup> for fluid milk fortified with 75 mg. of ascorbic acid per liter.

The data in Table II show that fast heating at high temperatures for the purpose of terminal disinfection of the infant feeding formula is less destructive of ascorbic acid than is slower heating at lower temperatures. There appears to be considerable loss of ascorbic acid during the heating procedure but during storage less loss is experienced than in unheated samples.

Slightly greater loss of ascorbic acid occurred in samples of the reliquefied product allowed to cool slowly to room temperature before being placed in the refrigerator than occurred in quickly cooled samples. Likewise, exposure of the formulas to diffused daylight accelerated destruction of the vitamin. This factor is primarily a function of light intensity; consequently, the degree of ascorbic acid destruction as influenced by this factor would be expected to vary from day to day.

The data in Table III show that the addition of 0.1 ppm. of soluble copper to the water used in making up the formulas had essentially no effect on the destruction of ascorbic acid during the heating of the formulas, but that 0.2 ppm. did accelerate the destruction slightly. Addition of larger quantities of copper to water used in the formulas caused drastic losses. It is interesting to note that heated formulas containing 0.2 ppm. copper suffered less ascorbic acid loss than did unheated formulas containing a like amount of copper, whereas heated samples containing 1 ppm. copper lost more of the vitamin than did the unheated samples containing 1 ppm. copper. The explanation for this fact is not readily apparent from these few data, but it may be that at low levels the effect of copper as an oxidative catalyst can be minimized by heat treatment, the copper possibly being bound by protein to form an inactive complex. At higher copper levels the destructive action of copper and heat appears to be additive.

The presence of 1 or 2 ppm. of added iron slightly increased the losses of ascorbic acid in heated formulas but concentrations of iron of these magnitudes seldom, if ever, would be found in water used in making up the formulas.

Chlorine in concentrations as high as 5 ppm. had no discernible effect on the loss of ascorbic acid during storage of the samples. In greater concentration a definite effect was noted. However, the residual chlorine content of the drinking waters of Columbus, Ohio, is usually less than 0.1 ppm. and in no instance is a 5 ppm. content to be expected in water used for making up a feeding formula.

#### SUMMARY

The following general observations are drawn from the data collected during the course of this investigation:

1. Loss of ascorbic acid in the dry powder contained in the opened can appears to be negligible during the first four days.
2. Reliquefied formulas made from dried milk products of the type used in these studies, containing approximately 75 mg. of total ascorbic acid per quart, and prepared in the conventional manner without heating, lose approximately 11 per cent (about 8 mg.) of their total ascorbic acid content during twenty-four hours of storage under ordinary home refrigeration.
3. Terminally disinfected formulas (originally containing about 75 mg. total ascorbic acid per quart) which have been rapidly cooled before being put under refrigeration lose approximately 15 to 20 per cent (about 11 to 15 mg.) of their total ascorbic acid content during the combined heating and storage period of twenty-four hours.
4. Terminally disinfected formulas allowed to cool slowly lose slightly more of their total ascorbic acid content than if cooled rapidly.
5. Terminal disinfection of the formula by the fast heating high temperature procedure is to be preferred with respect to the stability of ascorbic acid.
6. Warming the refrigerated formula quickly to body temperature just prior to feeding does not increase the loss of ascorbic acid.
7. Exposure of the reliquefied product to light for extended periods of time accelerates the loss of ascorbic acid and is to be avoided.
8. Iron and chlorine in the amounts normally present in treated city waters have no significant effect on the stability of the ascorbic acid in the formulas.
9. Contamination of the water used in making up the formulas with copper generally accelerates the loss of ascorbic acid. Therefore, boiling the water subsequently to be used in making up the formulas in copper vessels is not desirable.

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## Case Reports

### EMBRYOMA OF CONTRALATERAL KIDNEY TEN YEARS FOLLOWING NEPHRECTOMY FOR WILMS' TUMOR

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EMBRYOMA affecting both kidneys occurs rarely. Such involvement is manifested early or may be an incidental finding at necropsy (Walker,<sup>1</sup> Sheldon and Canaday,<sup>2</sup> Fusaro,<sup>3</sup> Campbell<sup>4</sup>). The origin of bilateral tumors is a matter of conjecture. Dean and Paek,<sup>5</sup> in referring to bilateral neoplasms in paired organs of children, question the use of the term *metastatic* because of the manner in which such tumors usually spread.

The case herein reported is of special interest and warrants presentation because the contralateral kidney was involved by embryoma ten years after nephrectomy for a similar tumor. Of additional interest is the fact that the patient died not as a direct result of the tumor but because of renal failure associated with diffuse renal fibrosis. Roentgen therapy apparently successfully destroyed the tumor tissue, but in so doing it is possible that it produced irreversible damage in the remnant normal kidney parenchyma.

W. A., a 10-year-old white boy, was admitted to the Pediatric Ward of the Graduate Hospital on Jan. 6, 1947, because of pain in the left flank of three days' duration and a vague history of an episode of hematuria which his mother attributed to trauma.

The past medical history revealed normal development until 5½ months of age when the patient became constipated and a mass was discovered in the right abdomen. A diagnosis of embryoma was made and confirmed by pathologic examination following right nephrectomy. (Fig. 1.)

The child progressed normally for approximately ten years, when pain occurred in his left flank and his mother felt a large tumor. He was admitted to the hospital three days later. On admission a large, firm, nontender mass was felt which filled the left abdomen from the costal margin to the crest of the ilium, and extended to the midabdominal area. The scar of the previous nephrectomy was evident in the right flank. Small, generalized adenopathy and an active ethmoiditis were discerned. The lungs were negative on physical examination. A systolic murmur was heard at the base of the heart. No cardiac hypertrophy was noted and the rhythm was normal. Blood pressure during this admission ranged between 130/70 and 134/90 mm. mercury. Funduscope examination was negative.

Urinalysis was negative on three occasions. The red blood cell count numbered 3,910,000 cells per cubic millimeter and the leucocytes 11,900 cells per cubic millimeter. The differential count was normal. Hemoglobin content of the blood was 11 Gm. per 100 c.c. (66 per cent). The hematocrit reading was 32 volumes per cent. Blood urea nitrogen was 18 mg., chlorides 584 mg., cholesterol 280 mg., and total protein 6.8 Gm. per 100 c.c. of blood, respectively. The carbon-dioxide combining power was 49 volumes per cent and the alkaline phosphatase 3.8 Bodansky units.

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An x-ray film of the abdomen showed an increased density in the left upper quadrant which could not be outlined definitely. Intravenous urography demonstrated good renal function but marked deformity of the upper calices and infundibula. The entire excretory system of the kidney was pushed downward and forward by a rather large mass. (Fig. 2.)

The patient's stay in the hospital was uneventful. His temperature, which was 101° F. orally on admission, continued in septic form until it fell by lysis to a normal level on Jan. 15, 1947. He was discharged Jan. 22, to be treated as an outpatient by the X-ray Department.



Fig. 1.—Microphotograph ( $\times 200$ ) showing glandular-like formation of the tumor mass involving the right kidney (nephrectomy performed June 21, 1937).

During the course of x-ray therapy he developed nausea, vomiting, headache, and increasing pallor. A blood count revealed 2,770,000 red blood cells per cubic millimeter with a hemoglobin content of 7.5 Gm. per 100 c.c. of blood. A total of 6,400 roentgen units had been administered to the tumor area when he was readmitted to the hospital on Sept. 29, 1947.

On this admission examination revealed generalized edema, extreme pallor, and slight nuchal rigidity. His weight was 72½ pounds, an increase of 11 pounds since his discharge on Jan. 22, 1947. A loud, systolic murmur was heard over the base of the heart and the second aortic sound was accentuated. Cardiac hypertrophy was evident on palpation and percussion. The blood pressure was 230/170 mm. mercury. No tumor mass could be felt in the abdomen. Funduscopic examination revealed pallor of both discs, exudate in the right retina and hemorrhage in the left.

Laboratory examination revealed a fixed specific gravity of the urine ranging from 1.010 to 1.013. The urines were acid in reaction and devoid of albumin. Blood urea nitrogen was 60 mg. per 100 c.c. of blood on admission and thereafter ranged to 125 mg. Blood creatinine, which was initially 3.4 mg. per 100

c.c. of blood, varied between 11 and 11.3 mg. The blood cholesterol was 268 mg. and cholesterol esters 186 mg. per cent. Blood calcium was 10 mg. per cent, phosphorus 3.3 mg. per cent, and alkaline phosphatase 2.2 Bodansky units. Serum bilirubin measured 0.3 mg., blood sugar 109 mg., plasma chlorides 556 mg. per cent, while total blood protein measured 5.6 Gm. per 100 c.c. of blood with an albumin value of 2.52 and a globulin value of 3.08 Gm. per cent, respectively. X-ray examination of the skeleton on Sept. 30, 1947, was negative for any evidence of metastases. The chest x-ray films showed a moderate degree of left ventricular enlargement with increased prominence of the aortic knob. The lungs were essentially negative. Intravenous urography failed to reveal any excretion of dye during an observation period of one hour and fifteen minutes, indicating a markedly decreased excretory function of the left kidney. An



Fig. 2.—Intravenous urogram revealing downward and forward displacement of left kidney (Jan. 7, 1947).

electrocardiogram on Oct. 8, 1947, revealed the following: The auricular and ventricular rate were both 108. The P-R interval was 0.12 second and a sinus tachycardia was evident. The P waves and QRS complexes were normal while the RS-T segments were elevated in CR<sub>2</sub>. The T waves were of low amplitude in CR<sub>2</sub> and CR<sub>3</sub>. These findings were interpreted to indicate some myocardial abnormality and probable left ventricular hypertrophy. The configuration of the T waves in the precordial leads suggested a high level of potassium in the blood.

During this admission the patient was oliguric and vomited at least once daily. His blood pressure ranged from 210/170 to 220/180 mm. Hg. He desired to be ambulatory, and in view of the obvious outcome, this was permitted until intense vertigo on Oct. 8, 1947, precluded him from leaving bed. The next day



he became unconscious. Examination revealed nuchal rigidity, opisthotonus, trismus, and contracted pupils. Tachycardia was present and the blood pressure was 260/170 mm. Hg. Breathing was stertorous and râles could be heard throughout the lungs. The spinal fluid was bloody and under considerable pressure. Therapy, which included two transfusions, hot packs, phenobarbital sodium and magnesium sulfate intramuscularly, and glucose and saline intravenously, was of no avail and he expired four hours after the onset of coma, Oct. 9, 1947.

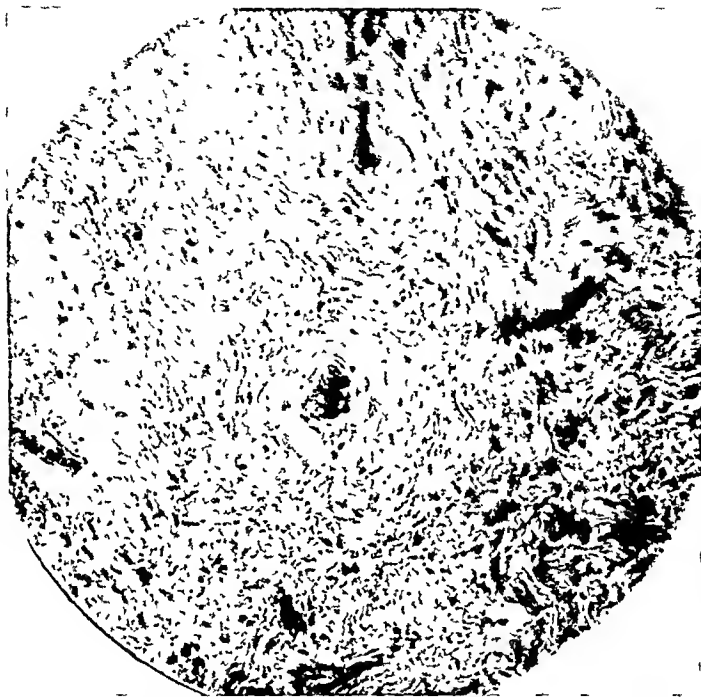


Fig 3 —Microphotograph ( $\times 200$ ) of tissue obtained at autopsy from small tumor mass on mid-anterior surface of left kidney (Note marked fibrosis)

Autopsy was restricted to the left kidney area and was done by Dr. L. L. Adamkiewicz. The abdominal cavity contained about 200 c.c. of clear, straw-colored fluid. Diffuse congestion was noted in the omentum. The left kidney weighed 240 Gm., was normal in outline, and was not adherent to surrounding tissues. The left adrenal was markedly compressed and weighed 3 Gm. The kidney measured 14 cm. in length, 6.5 cm. in width, and 3.5 cm. in thickness. A yellowish tumor, slightly raised and buttonlike, and measuring 2.5 cm. by 2.5 cm., was found 6 cm. from the lower pole on the mid-anterior surface. (Fig. 3.) On section a large tumor mass measuring 6 cm. by 6.5 cm. by 3.5 cm. with a necrotic center was seen in the substance of the upper pole of the kidney. The tumor was pale yellow in color and uniform in texture beyond the necrotic center. It was infiltrative and a wide, fibrous band separated it from the kidney tissue. Microscopic examination showed an alveolar arrangement of slightly oval cells with a small amount of cytoplasm. These cells were of uniform size and mainly of low cuboidal shape. The nuclei stained moderately deep and showed occasional small nucleoli. Fibrous tissue, composing a supporting stroma, surrounded the epithelial cells, which were single or in acinar formation. There were also wide bands of fibrous tissue encapsulating the growth. The latter

was invaded by collections of round cells and a few plasma cells. There were many areas of calcification in the fibrous tissue capsule. The cellular elements often seen in this type of tumor were no longer evident, possibly as a result of the intensive x-ray therapy. The microscopic picture was one of marked fibrosis. The necrotic area in the central portion of the growth had the characteristics of necrosis due to deficient blood supply. The smaller tumor had the same morphology as the larger one except that no necrosis was present. The outstanding picture in the kidney was that of an extensive arteriolar nephrosclerosis with extensive hyalinization.

#### DISCUSSION

Prognosis following nephrectomy because of embryoma depends on recurrence and metastases. In a series of sixty cases reported by Ladd and White,<sup>6</sup> recurrence occurred in thirty-two instances and of these thirty-one occurred within nine months after operation. The longest interval for recognition of recurrence was twenty months. The postoperative mortality rate within a three-year period is variously reported to range from 42 to over 70 per cent (Ladd and White,<sup>6</sup> Priestley,<sup>7</sup> Nesbit and Adams,<sup>8</sup> Higgins and Shively<sup>9</sup>) with one survival up to 41 years. (Higgins and Shively.<sup>9</sup>) Embryoma occurring in a contralateral kidney approximately ten years after nephrectomy for a similar tumor is a rare occurrence.

Tumors of this variety are notoriously radiosensitive and roentgen therapy is at times employed preoperatively and postoperatively. It remains the only form of treatment in cases not amenable to surgery. In our case the x-ray therapy may have contributed to the development of sclerosis and fibrosis and thereby accelerated the progression of the disease process in the remnant kidney. The establishment of an artificial kidney mechanism was considered but was not deemed suitable in a situation of this nature.

#### SUMMARY

1. A case is reported in which a contralateral kidney was apparently involved by embryoma approximately ten years after nephrectomy for a similar tumor.
2. Roentgen therapy produced a remarkable reduction in the size of the tumor but may have contributed to the fibrosis and other changes which finally resulted in the death of the patient from renal failure.

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# BILATERAL OPTIC NEURITIS FOLLOWING CHICKEN POX

## REPORT OF CASE WITH APPARENTLY COMPLETE RECOVERY

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NEUROLOGICAL symptoms after chicken pox are relatively rare. A great variety of symptoms have been reported, including unconsciousness, delirium, tremors, ataxia, cerebellar syndromes, spinal paraplegias, etc. Cranial nerve palsies have occurred, usually combined with other symptoms. Involvement of the optic nerve has been reported by Ford. Bilateral involvement of the optic nerves without other symptoms may not have been seen. This case is presented because of its rarity and interest.

### CASE REPORT

About March 28, 1948, a 5-year-old white male child developed chicken pox. He had a generalized eruption but was not particularly ill. He was restricted to bed for the first week and his convalescence seemed uneventful.

Two weeks after the onset, he was heard to complain that it was dark outside and the next day he complained of darkness in the house. Within the next few days he became unable to find food set in front of him and was unable to find the fork and spoon to eat.

The early development and family history are irrelevant.

Physical examination showed a well-developed, well-nourished child of 5 years, weight  $44\frac{1}{2}$  pounds, height  $44\frac{1}{2}$  inches, temperature  $99.2^{\circ}$  F. (R). Eyes showed bilaterally engorged retinal veins and elevated discs. Vision, especially central vision, was markedly impaired. He was able to distinguish dark and light, but fingers held before the eyes could not be counted.

The remainder of physical examination was essentially negative. There were no stiff neck, reflex changes, or other nerves involved.

The patient was seen by a local ophthalmologist who confirmed the eye findings and recommended neurological consultation because of the possibility of an intracranial neoplasm. We believed it to be a postvaricella encephalitic picture limited to the optic nerves. Because of the rarity of this condition, the child was sent to the Pediatric Department of the University of Utah Medical School, where he was examined by Dr. C. Harrison Snyder of the Department of Pediatrics and Dr. Alan Crandall of Ophthalmology Department. Their findings confirmed the visual changes and an elevated disc of  $3\frac{1}{2}$  D. bilaterally with appearance of papillitis.

Laboratory studies on April 18, 1948, revealed hemoglobin of 16.2 Gm. per 100 c.c. and red blood cells 6,010,000 per cubic millimeter. The hematocrit was 44 per cent packed cells, with an Wintrobe erythrocyte sedimentation rate of 5 mm. per hour. White blood count was 12,700, polymorphonuclears were 47 per cent, eosinophiles 2 per cent, basophiles 1 per cent, lymphocytes 47 per cent, and monocytes 3 per cent. Examination of the spinal fluid showed a pressure of 165 mm. of water, Queckenstedt sign was normal bilaterally, there were no cells, negative Pandy, and normal protein. Electroencephalogram was within normal limits.

The vision remained very poor for two weeks and then began to improve very slowly. Within a week after the vision had begun to return, a test of

20/50 was obtained in each eye. Six weeks after the beginning of the blindness 20/30 vision was found bilaterally and the nerve heads were practically normal in appearance.

Thereafter no further improvement in vision occurred. The patient felt well subjectively all the time. The vision previous to the illness was not known.

#### SUMMARY

The case is presented of a 5-year-old child with bilateral optic neuritis developing marked impairment of vision two weeks after chicken pox. There was almost complete recovery within two months.

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## CONGENITAL ABSENCE OF THE PATELLAE

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**I**NTERMITTENTLY, during the past fifty years, cases of congenital absence or dysplasia of the patellae associated with dystrophy of the nails and impaired function of the elbows have been reported in the medical literature. This triad is both hereditary and congenital. Almost all of the cases reported have a marked familial occurrence which indicates the hereditary etiology. It is apparently caused by a developmental defect of the mesodermal and ectodermal layers of the embryo.

Aschner<sup>1</sup> in 1934 offered an explanation as to why these defects occur separately or together in an individual. It is assumed there are separate pathologic factors responsible for each part of the triad since each may occur alone without the other. There is a close linkage in the same chromosome between the two genes which result in congenital patellar defects and dystrophy of the nails. Because of this close linkage, these two defects are almost always inherited together when present in a family. There is also a third pathologic factor which causes luxation of the head of the radius. This factor is in close proximity to the other two but not as close as the other two are to each other. For this reason luxation of the head of the radius does not occur as frequently as dystrophy of the nails and patellar defects. One can understand, therefore, why these three congenital defects can occur together or separately in the same individual or family.

In reviewing the literature, Senturia<sup>4</sup> and Mino and his collaborators<sup>2</sup> indicate that congenital absence of the patella has been reported almost invariably in association with one or both of the defects described above. Its occurrence alone is rare. The case here reported is unique because there is congenital absence of both patellae with no evidence of abnormality of the elbows or dystrophy of the nails. Three other siblings were examined but none of the defects of this triad was present. From the history obtained from the child's mother, the maternal family has been free of evidence of the triad. The only suspicion of its occurrence elsewhere in the child's family is found in a statement by the mother which indicated that the father of the child had "weak knees." Due to the separation of the parents, the present whereabouts of the father could not be ascertained.

### CASE REPORT

S. C., a Negro girl, aged 9 years, was brought to the clinic by a welfare worker for a routine physical examination in September, 1948. At this time it was noted that the patient had no palpable or visible patellae.

From the Department of Roentgenology, Baltimore City Hospitals.

She is one of four living children, all of whom are well. One other child is dead. The father is living and well but has "weak knees." The mother is a patient in a tuberculosis sanitarium.

The birth history and habits are entirely noncontributory.



Fig. 1—Genu valgum deformity

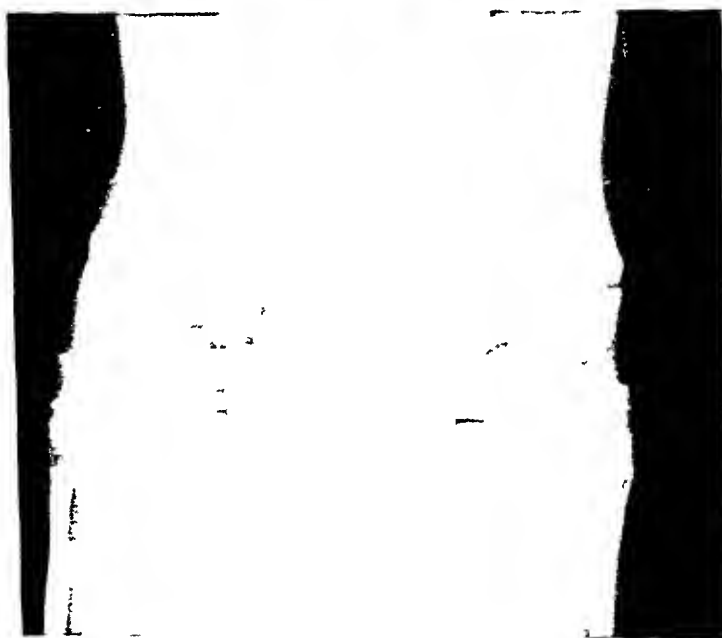


Fig. 2—Complete absence of both patellae, anterior view.

There is a history of measles, mumps, chickenpox, pertussis, and tonsillitis. It is known that the child has had "weak knees" since an early age because of her many falls.

On physical examination, she is 52 inches in height and weighs 52 pounds. In general she is rather undernourished. The only other positive findings are

as follows: There is some atrophy of the lower extremities. The knees appear rather flat anteriorly (Fig. 1) and the patellae are not palpable. There is a genu valgum deformity (Fig. 1). There is a faint basal systolic murmur audible over the heart. The lungs are clear. The spleen is barely palpable. The fingernails are normal. The child has full flexion of the elbows and they are normal in appearance.

X-ray examination of both knees verifies the absence of both patellae (Figs. 2 and 3). X-ray examination of both elbows shows no evidence of abnormality.



Fig. 3.—Complete absence of both patellae, lateral view.

#### SUMMARY

A unique case of congenital absence of the patellae in which there are no other associated abnormalities is presented. A brief review of the literature is presented with special reference to the explanation of the cause of this developmental defect.

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# Clinical Conference

CONFERENCE AT THE NEW YORK HOSPITAL-CORNELL  
MEDICAL CENTER

JAN. 14, 1949

SAMUEL Z. LEVINE, PEDIATRICIAN-IN-CHIEF

DR. LEVINE.—According to our usual custom, the patient will not be in the room during the recounting of the history, physical and laboratory findings, and course in the hospital, but will be shown later. Dr. Mosher will present the first case.

## Case 1. Hyperinsulinism

DR. THOMAS E. MOSHER (Resident in Pediatrics).—A. W., a white boy of 6½ years, is being presented on his third admission to the New York Hospital. He was first admitted at the age of 4½ years. The present illness apparently started shortly after birth. At 2 days of age he became comatose; there was no cyanosis or convulsions and he roused spontaneously after twelve hours. He thrived until 9 months of age when he had an uncomplicated pneumonia. At 10 months the patient had an episode of persistent vomiting and was hospitalized for three days; this symptom ceased following an infusion. At 14 months he had measles and again was hospitalized. From 2 to 3 years of age he had three episodes of persistent vomiting and drowsiness lasting two to three days. At 3 years of age these episodes became more severe and at times the boy could not be aroused. From 4 to 4½ years the attacks occurred every two weeks and by this time were characterized by two to three days of forgetfulness, clumsiness, stammering speech, awakening at night, vomiting, persistent drowsiness, and hypoglycemia.

The patient was admitted to the New York Hospital in January, 1947, at the age of 4½ years. Physical examination was unrevealing; roentgenograms of the skull, abdomen, and long bones were normal; electroencephalogram was essentially normal; a psychometric examination showed low average intelligence. His oral glucose tolerance test (2.2 Gm. per kilogram) was as follows:

Fasting	92 mg. %
½ hour	162 mg. %
1 hour	149 mg. %
2 hours	119 mg. %
3 hours	42 mg. %

His insulin sensitivity test (½ U per kilogram) was:

Fasting	89 mg. %
½ hour	42 mg. %
1 hour	31 mg. %
2 hours	26 mg. %



At the end of two hours he became drowsy and glucose was administered. His adrenalin tolerance test (0.01 ml. of 1:1000 per kg.) revealed:

Fasting	73 mg. %
$\frac{1}{2}$ hour	97 mg. %
1 hour	114 mg. %

His starvation test was as follows:

Fasting	87 mg. %
18 hours	62 mg. %
24 hours	36 mg. %
26 hours	29 mg. %

It was decided first to try medical management and he was sent home on a high protein diet and desiccated thyroid 15 mg. per day. The thyroid was discontinued by his private physician after a month. The patient was asymptomatic for five months; following a pharyngitis he again began to have the previously described episodes once a month and then with increasing frequency until at 5 years of age he had them twice a week. These were relieved by glucose infusions.

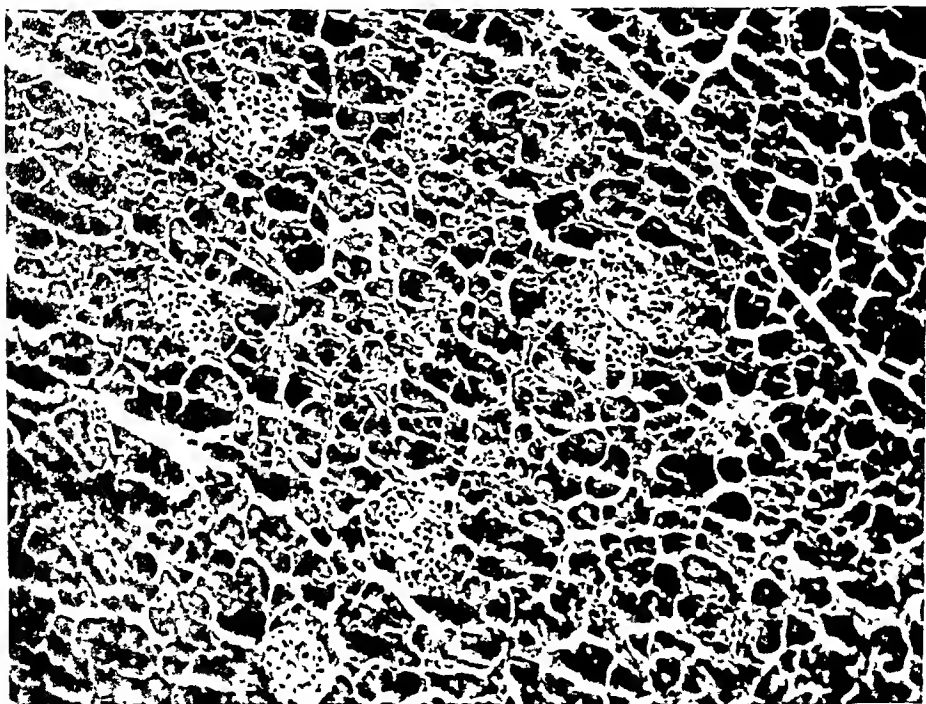


Fig. 1.—Case 1. Microscopic section of pancreas, January, 1948.

During his second admission to the New York Hospital in January, 1948, at 5½ years of age, all of the previous tests were repeated with essentially similar results. The I.Q. again was within the average range. Exploration was

decided upon but no pancreatic tumor was found. Approximately two-thirds of the pancreas was excised and microscopic sections revealed unrestricted proliferation of the islets of Langerhans, as many as 17 islets being seen in one low-power field (Fig. 1). The boy's postoperative course was uneventful. Repeat blood studies two weeks postoperatively showed no significant change from the initial values. He was sent home on a high protein diet. He was free from serious seizures for ten months following the operation, when he again lost consciousness, and following adrenalin and glucose he vomited and was drowsy the rest of the day. Thereafter these episodes recurred weekly and he was readmitted twelve days ago on Jan. 6, 1949, at 6½ years of age, one year following operation. Glucose, insulin, and adrenalin tolerance curves are essentially unchanged from those on his first admission. His electroencephalogram remains normal and his psychometric test, as before, shows a low average intelligence. During this two-week period of hospitalization he has had no seizures except those brought on by the insulin tolerance test.

DR. LEVINE.—There are two good reasons for presenting this patient. One is a consideration of differential diagnosis, which I hope Dr. Schloss will discuss in some detail. The other is the problem of therapy. Was exploratory laparotomy indicated and what should be our next therapeutic approach?

(Patient is brought in in a wheel chair)

DR. OSCAR M. SCHLOSS (Professor of Clinical Pediatrics).—Hello, Alan. How do you feel?

PATIENT.—Fine.

DR. SCHLOSS.—You can all see that this boy looks pretty well. He is a little undersized and slightly underweight. Inspection of his abdomen shows a transverse infraumbilical scar, the result of his operation done about a year ago. Are there any questions anyone would like to ask before he goes out?

STUDENT.—On what sort of diet is the patient now?

DR. MOSHER.—A high protein diet.

STUDENT.—Is his appetite normal or excessive?

DR. SCHLOSS.—Alan can answer that one. How is your appetite, Alan?

PATIENT.—It's O.K., I guess.

(Patient is taken out)

DR. SCHLOSS.—At the time of the first admission to this hospital it was already known that the patient suffered from recurring attacks of hypoglycemia accompanied by characteristic symptoms. He was admitted here with the thought that these episodes were perhaps due to a greatly increased or unopposed secretion of insulin and perhaps belonged to the group of cases amenable to surgery. Before this diagnosis could be seriously entertained it seemed necessary to exclude other causes of hypoglycemia by further observations and tests.

By most writers hypoglycemia of clinical importance is divided into the cases due to functional causes (actually of undisclosed origin) and those due to organic disease of organs participating in the intricate mechanism of sugar mobilization and metabolism.

At the outset it seemed possible to remove this boy's disease from the category of functional hypoglycemia. In the first place, his symptoms were more dramatic and severe than usually occur in the functional cases. In addition, his attacks occurred only after a long fast and not three to four hours after a carbohydrate meal. Also, his fasting blood sugar was frequently very low, which is rarely if ever observed in functional hypoglycemia, in which the lowest blood sugar usually appears after the insulin-stimulating effect of carbohydrate ingestion. It, therefore, seemed necessary to explore the organic diseases which could be responsible for this patient's hypoglycemic attacks.

There was no evidence from the history, laboratory tests, or examination that he was affected by the type of organic liver disease which may cause hypoglycemia. Furthermore, the normal size of the liver, the absence of ketone substances in the urine, and a positive response to the epinephrin test seemed sufficient to exclude the type of disease associated with immobility of liver glycogen seen in von Gierke's disease.

No disease or disturbance of function of the thyroid, adrenal cortex, or pituitary gland was disclosed and we felt that these causes of hypoglycemia could be excluded with reasonable assurance. There were no symptoms or physical signs, neurologic or otherwise, which seemed consistent with a thalamic lesion.

By this process of exclusion and by the positive evidence which has been presented in the history, laboratory tests, and clinical observations it seemed justifiable to infer that the attacks of hypoglycemia and attending symptoms from which this patient suffered arose from an increased action of insulin. There are two possible mechanisms through which this could occur. It has been demonstrated that both the pituitary and the adrenal cortex elaborate hormones which are insulin antagonists, and it seems possible that a defect in such restraining influences might lead to an unopposed and enhanced insulin effect which could produce severe hypoglycemia even in the absence of demonstrable pancreatic disease or the secretion of grossly abnormal amounts of insulin.

The second possibility involved the actual presence of pancreatic disease. A review of this patient's history discloses the occurrence of diagnostic data which, according to Whipple's criteria, usually designate the presence of adenoma of the islands of Langerhans. An important diagnostic point is that the symptoms provoked by hypoglycemia follow a pattern which is duplicated essentially in all attacks. In a patient who displays a definite pattern of symptoms there is, first, the history of attacks occurring during the fasting state; second, during the attack or after a prolonged fast the blood sugar falls below 50 mg. per cent; and, third, the patient becomes symptom-free immediately on the intravenous administration of glucose. According to Whipple's statistics about 80 per cent of the adults whose disease fulfilled these diagnostic criteria were found to have operable islet tumors.

It was on the strength of this evidence that this patient was subjected to operation, although we knew at the time that typical islet adenomata are practically unknown in children. Nevertheless, since severe and repeated attacks of hypoglycemia can lead to irreversible brain damage, it seemed proper that the patient be given the benefit of every doubt. Accordingly, an exploratory

operation was done. As you have heard, no tumor was found but a partial pancreatectomy was performed. Histologic examination of the removed pancreatic tissue showed considerable hypertrophy of the islets, a condition which duplicates what has been found occasionally in children and frequently in adults who have suffered from severe hypoglycemia. Although no islet tumor was found, it would seem that the great increase of islet tissue would justify the diagnosis of organic hyperinsulinism.

DR. LEVINE.—Are there questions about the diagnosis?

ASSISTANT RESIDENT.—I should like to ask Dr. Schloss whether there is any way of differentiating preoperatively between adenoma of the pancreas and diffuse hypertrophy of islet tissue?

DR. SCHLOSS.—There is apparently no clinical means of doing so. What, if any, is the exact relationship of the two conditions cannot be answered now. It is conceivable that the etiology of the two conditions may be dissimilar despite the fact that they cause identical symptoms. The true adenoma may be a neoplasm while the diffuse hypertrophy could be a response to the stimulative effect of a hormone secreted by another endocrine gland. This would be somewhat analogous to the type of Grave's disease caused by the thyrotropic hormone of the pituitary.

DR. LEVINE.—Now we are faced by the problem of therapy. After the partial pancreatectomy there was apparent improvement, with almost complete absence of symptoms for ten months. As Dr. Schloss has said, the reasons for the operation were first, that without it we could not rule out a tumor, though pancreatic adenomas are admittedly exceedingly rare in childhood; and, second, the danger of mental deterioration as a result of repeated seizures.

The recurrence of the seizures brings up the question of further surgical treatment versus medical treatment. Dr. Schloss, what is your opinion about this?

DR. SCHLOSS.—Reports in the literature of cases in whom successive partial pancreatectomies have been performed have been very discouraging. Dr. Levine, have you ever seen a case where this has finally resulted in a cure?

DR. LEVINE.—Never, in children, where no adenoma has been present.

DR. SCHLOSS.—As for medical treatment, the patient could be treated with alloxan. As you know, this substance causes destruction of the islets and has been used experimentally to produce diabetes in laboratory animals. It has been used in the treatment of humans suffering from hyperinsulinism caused by diffuse islet hypertrophy. Talbot has reported improvement of one patient following its use. This drug, however, is very toxic and can produce severe kidney and liver injury. I think I should prefer to hold it in reserve until more is known of its usefulness and dangers or until all other measures have failed and its employment seems imperative as a last resort. The third course would be to treat the boy symptomatically and this at the moment seems the method of choice. We will give him larger amounts of carbohydrate and at frequent intervals. This regimen has proved useful in similar cases. At the onset of hypo-

glycemic symptoms, which are clearly recognized by his mother, glucose will be given by intravenous injection.

VISITING DOCTOR.—May I ask Dr. Schloss whether he is at all afraid of changing from a high protein to a high carbohydrate diet? Is there any danger in giving too much carbohydrate?

DR. SCHLOSS.—No doubt you refer to the possibility of overstimulation of insulin production. In the functional hypoglycemias such as one sees in adults with no organic cause demonstrable, there is ample evidence that high carbohydrate diet makes them worse. In contrast to this patient, the blood sugar in these functional cases rises after a carbohydrate meal and then makes a sharp drop within one to four hours (usually two to three hours) accompanied by symptoms. This boy's low point in blood sugar comes with prolonged fasting. It would seem that suitable dietary management in this case would consist of frequent small meals of fairly high carbohydrate content, with extra carbohydrate when prodromal symptoms suggest its need, in order to ward off attacks. If he can be kept comfortable and free from severe attacks it is possible that there will be discovered some method of hormonal control of the islet hypertrophy or even a direct insulin antagonist of therapeutic value.

## Case 2. Congenital Adrenocortical Insufficiency With Virilism

DR. WARREN TEPPER (Assistant Resident in Pediatrics).—This white male infant, born Oct. 27, 1948, was admitted to the pediatric service of The New York Hospital on November 27 because of vomiting and poor weight gain. His parents were first cousins and of Italian descent. The mother was 28 years old. The pregnancy, except for spotting for one week in the first trimester, and the birth were normal. In the nursery the infant vomited small amounts of formula frequently; this persisted after discharge on the sixth day. At 10 days of age he became cyanotic during bubbling, was admitted to another hospital and put in an oxygen tent. Right-sided tremors were noted and a blood culture was positive for hemolytic *Staphylococcus aureus*. The culture became sterile following a course of intramuscular penicillin in high dosage but the vomiting continued. Lumbar puncture, subdural tap, gastrointestinal series, and barium enema were all negative. A roentgenogram of the chest on the fifteenth day of life demonstrated a left pneumothorax which cleared spontaneously. Two weeks after admission he had another transient episode of cyanosis. Despite a good appetite daily parenteral fluids were required to prevent dehydration. In the week prior to admission to The New York Hospital he had four to six loose, green, foul stools daily which diminished in frequency on a protein milk formula. At one month, he weighed 9 ounces less than at birth and was transferred to The New York Hospital.

Examination revealed an extremely malnourished and dehydrated infant. He was active but irritable and sucked his fists hungrily. His respirations were shallow and rapid. The skin was olive-brown and mottled with fair turgor; the subcutaneous fat deposits were markedly depleted and the skin hung in folds which were particularly prominent along the inner aspect of the thighs. There

was a papular, erythematous, scaly eruption on the scalp. The anterior fontanel was open, 3 by 5 cm., and depressed; the posterior fontanel admitted a fingertip. The abdomen was distended and tympanitic and the liver edge was palpable 3 cm. below the costal margin in the midcostal line. The spleen and kidneys were not felt. The penis seemed comparatively large. The testes were in the scrotum, were of normal size, and had a firm feel. The prostate was not palpable by rectal examination. The extremities were cold and faintly cyanotic. There was no fever or sign of infection. Physical measurements were as follows: weight, 2,820 Gm.; head circumference, 35.5 cm.; chest, 33 cm.; abdomen, 32 cm.; stem length, 35 cm.; total length, 55 cm. His appearance is shown in the first slide (Fig. 2).



Fig. 2.—Photograph of baby taken at 5 weeks of age, Dec. 2, 1948.

Laboratory tests demonstrated a negative urinalysis. The blood counts and differential showed hemoglobin 22 Gm.; red blood cells 6,400,000, white blood cells 7,100; differential: 66 per cent lymphocytes, 4 per cent eosinophiles, 30 per cent polymorphonuclears. On fluoroscopic examination the heart appeared undersized and its transverse diameter was estimated to be one-third that of the thorax.

Chemical examination of the blood on Nov. 27, 1948, showed: potassium 7.9 mM per liter, sodium 130 mM per liter, bicarbonate 20 mM per liter, calcium

TABLE I. MALE INFANT WITH ADRENOCORTICAL INSUFFICIENCY AND VIRILISM

PERIOD		WEIGHT* (Gm.)	CONCENTRATION IN SERUM*						TREATMENT*					DESOXY- CORTICO- TERRONE ACETATE (MG./ DAY)
DATES	DURA- TION (DAYS)		SODIUM (mM./L.)	POTAS- SIUM (mM./L.)	CHLORIDE (mM./L.)	BICARBO- NATE (mM./L.)	PROTEIN (GM./ 100 mL.)	UREA N (MG./ 100 mL.)	GLUCOSE (MG./ 100 mL.)	FLUID PER PAREN- TERAL (ML./DAY)	ADDED NaCl (GM./ DAY)	ADDED Na LAC- TATE (GM./ DAY)	ADRENAL CORTICAL EXTRACT (ML./ DAY)	
1948-12/1	3	2,380	118	6.3	98	19	7.6	56	36	430	0.8	-	-	-
12/2-12/3	1	2,350	134	4.7	114	15	6.5	-	-	480	3.3	-	22	-
12/4-12/6	2	2,520	119	9.5	101	21	7.6	15	56	260	4.9	1.1	11	-
12/7-12/10	3	2,630	120	7.8	92	30	6.7	-	-	585	6.6	2.8	18	2
12/11-12/13	2	2,740	141	5.0	101	23	6.1	-	-	580	5.3	0.5	20	4
12/14-12/20	6	2,800	132	6.1	98	29	6.7	-	-	870	5.0	0.5	10	4
12/21-1/7	16	3,760	138	4.9	107	25	4.9	-	-	770	5.0	0.5	-	5
1/8-1/18	10	4,088	132	5.4	107	27	5.4	-	-	710	5.0	0.6	-	2
1/18-1/24	6	4,451	143	5.1	110	27	5.7	-	76	766	3.5	0.8	-	2
1/25-1/29	4	4,479	141	6.3	111	22	5.9	-	88	743	3.5	0.8	-	-
1/30-2/1	2	4,380	135	8.1	107	-	-	-	-	729	1.4	0.4	-	-
2/2-2/5	3	4,338	140	6.1	104	22	-	14	-	695	1.4	0.4	-	2
2/6-2/16	10	5,020	138	5.5	108	25	5.6	-	92	723	3.5	0.8	-	2
2/17-2/23	6	5,180	133	5.8	112	-	-	-	-	685	3.5	0.8	-	1
2/24-2/25	1	5,380	-	-	-	-	-	-	-	750	3.5	0.8	-	2

\*The values for weight, concentration in serum, and treatment are those on the last day of the period stated and represent approximately the values obtaining throughout the period.

10.7 mg. per 100 ml., phosphorus 5.3 mg. per 100 ml., blood urea nitrogen 24 mg. per 100 ml.

The relation of the more important examinations of the serum to the type of treatment given during the three-month period in the hospital is shown on the blackboard (Table I).

Despite the absence of diarrhea and vomiting from November 28 to December 1, it may be seen that a customary food intake with small amounts of parenteral fluids and added salt was associated with a progressive loss of weight and a reduction in serum sodium, chloride, and bicarbonate, elevation of blood urea nitrogen and increasing clinical signs of dehydration and collapse. Large quantities of parenteral fluids and added sodium chloride were started on December 2 and the infant was given 22 ml. per day of adrenal cortical extract. By December 4 the serum potassium had fallen and the sodium and chloride levels had risen but the bicarbonate content was still reduced, there was no weight gain and only slight clinical improvement. Even the chemical improvement was not maintained on this regimen, as shown by the fall of serum sodium to 119 and the rise of serum potassium to 9.5 mM per liter on Dec. 6, 1949. During this period the infant was almost moribund on several occasions. Daily intramuscular injections of desoxycorticosterone acetate in oil in a dosage of 2 mg. were begun on Dec. 7, 1948. This was increased to 4 mg. daily on December 10 and by December 14 on this dosage of desoxycorticosterone acetate combined with 20 ml. per day of adrenal cortical extract, 5 Gm. of added sodium chloride, 0.5 Gm. of sodium lactate, and total fluids up to quantities of 350 ml. per kilogram, chemical control and real clinical improvement occurred. The latter was manifested by disappearance of the signs of dehydration, improvement in peripheral circulation, and by the general appearance of the infant. During the period from December 14 to December 20, parenteral fluids were discontinued and the adrenal cortical extract was progressively decreased from 20 ml. per day until it, too, was discontinued, at which time the dosage of desoxycorticosterone acetate was increased from 4 to 5 mg. The infant showed rapid progress with marked weight gain during this period. On Jan. 8, 1949, the dosage of desoxycorticosterone acetate was decreased to 2 mg. daily and on a customary formula with the addition of 3.5 to 5.0 Gm. of sodium chloride and 5 to 7 ml. of molar sodium-lactate, the infant continued to thrive. Between January 25 and February 1, when desoxycorticosterone was withdrawn and the amount of added sodium decreased, the infant again lost weight and showed signs of dehydration and poor peripheral circulation associated with a slight but significant fall in serum sodium and a rise in serum potassium. As shown in the table, these changes were again reversed on resuming injections of desoxycorticosterone acetate and increasing the amount of added sodium. During the period of February 17 to 23, when the dosage of desoxycorticosterone acetate was reduced to 1 mg. daily, there was no striking change in the serum chemistry but the infant was less active, ate poorly, gained weight more slowly, and looked less well. Increasing the daily dosage to 2 mg. on February 24 was again associated with clinical improvement.

(The infant was brought in. See Fig. 3.)



DR. S. Z. LEVINE.—You can see that at 4 months this baby appears healthy and well nourished. The contrast with his appearance on admission, as you saw it in the photograph, is striking. The testes feel firm though not large. Recently, long, fine dark hair has appeared on the side of the face down to the level of the mouth. Although this is not more than is seen in some infants with no virilism, it is unusual in that it appears to be increasing rather than decreasing.

Dr. Tepper, has a recent rectal examination been done?

DR. TEPPER.—Yes, sir, by Dr. Barnett.



Fig 3 —Photograph of baby taken at 4 months of age, Feb. 21, 1949.

DR. HENRY L. BARNETT (Assistant Professor of Pediatrics).—I palpated a suggestive mass in the region of the prostate.

DR. LEVINE.—Are there questions about the story so far, before the infant is taken out?

VISITING DOCTOR.—Was any other therapy given besides that described?

DR. TEPPER.—Yes. During this extended period the infant received several blood transfusions and was given penicillin and aureomycin for short periods because of mild respiratory infections. He received various forms of evaporated milk formulas, added vitamins A, C, and D, and at 3 months was started on solid foods. There has been no indication that these measures or any factors other than those shown in the chart had any specific influence on the progress of the infant.

VISITING DOCTOR.—What other laboratory studies were made?

DR. TILPNER.—Repeated electrocardiograms showed changes which correlated with and were interpreted as being due to changes in potassium. These changes included elevation of the T wave during periods of hyperpotassemia and a decreased voltage in all deflections during periods of desoxyeorticosterone acetate injection. Determinations of 17-ketosteroids for two twenty-four hour periods, done in Dr. Ephraim Shorr's laboratory, showed 3.78 and 5.70 mg. per twenty four hours. Injection of 85 mg. of adrenocorticotrophic hormone showed no decrease (patient: plus 1 per cent, control: minus 89 per cent) in circulating eosinophiles and no significant increase (patient: plus 10 per cent, control: plus 65 per cent) in the urine acid-creatinine ratio after four hours. He was given the Cattell Infant Intelligence scale at the age of 3½ months by Miss Elizabeth New. He scored a mental age of 4 months which is slightly ahead of his chronological age and seems to indicate that at the present time his intellectual development is on the high average level.

Roentgenograms demonstrated no intra-abdominal masses or calcification, and bone age was interpreted as within normal limits. Repeated blood counts have been within normal limits except for an unexplained eosinophilia and relatively high percentage of lymphocytes.

DR. LEVINE.—At the time of admission, the appearance of this infant was characteristic of the type of severe malnutrition and dehydration in a one-month-old infant which could have been produced by a variety of conditions. It soon became apparent, however, that the underlying cause for the failure of this infant to thrive was an unusual one, and even after it was determined, the proper course of treatment presented many problems. Dr. Barnett, Miss McNamara, Dr. Hare, and their group have just completed an extensive series of observations directed toward elucidating some of the problems involved, and Dr. Barnett will discuss this patient and describe some of their results.

DR. BARNETT.—When seen here at one month of age, this infant presented certain unusual features which led Dr. Mosher first, I believe, to suspect that he might be suffering from adrenal insufficiency. His failure to thrive, the episodes of collapse, and the extreme degree of dehydration and anhydremia were not adequately explained by the history and findings. The probability of this diagnosis being right was increased when the serum was found to contain a high level of potassium and a low level of sodium, and further, by failure of large quantities of water and sodium to correct these chemical changes and the dehydration even in the absence of diarrhea or vomiting. His subsequent dramatic response to desoxyeorticosterone acetate and added salt, the reappearance of the symptoms and findings with their withdrawal and the absence of response to adrenocorticotrophic hormone, all served finally to establish the diagnosis of adrenal insufficiency. Although his penis is relatively large and there appears to be beginning abnormal growth of facial hair, these two possible manifestations of virilism are not definite enough to be certain that they do not represent normal variation. However, the urinary excretion of 4.7 mg. of 17-ketosteroids per twenty-four

hours is elevated to the level normally found by Talbot and associates<sup>1</sup> in pre-pubertal boys so that enlargement of the penis, growth of facial hair, deepening of the voice, aene, excessive growth and muscular development, and epiphyseal closure are expected to occur precociously. It seems clear, then, that this boy has the type of adrenal disease first recognized and described in 1939 by Butler, Ross, and Talbot<sup>2</sup> and by Wilkins, Fleischmann, and Howard,<sup>3</sup> in which there is insufficiency primarily of the electrolyte controlling hormone or hormones and an excess of the androgenic hormone of the adrenal. Thelander and Choffin,<sup>4</sup> Bratrud and Thompson,<sup>5</sup> and Darrow,<sup>6</sup> have described additional infants with this syndrome and although many aspects of it remain unclear, certain concepts have emerged. In all instances in which the adrenals were examined, bilateral hyperplasia was found. This type of hyperplasia is recognized more frequently in girls in whom it produces pseudohermaphroditism. It is of interest, however, as pointed out recently by Wilkins,<sup>7</sup> that of the eighty-three reported cases of female pseudohermaphroditism due to congenital hyperplasia, associated adrenal insufficiency is known to have occurred in only six, whereas of sixteen males with the same disturbance, ten had evidences of such insufficiency. It seems possible that the apparent greater incidence of congenital bilateral adrenocortical hyperplasia in females may stem from the fact that pseudohermaphroditism is apparent at birth and is less frequently associated with adrenal insufficiency whereas in boys virilism is not manifest at birth and many may have died from the more frequently associated adrenal insufficiency before virilism had appeared and, therefore, without being recognized as adrenocortical hyperplasia. A further important fact to be learned from the reported cases of adrenal insufficiency with virilism is that in well over one-half of them congenital adrenocortical hyperplasia occurred in other siblings, manifesting itself by similar findings in brothers or pseudohermaphroditism in sisters.

I should like to point out some features of the condition exemplified by the infant we are presenting today. From the table it may be seen that despite an initial response to adrenal cortical extract with added intake of sodium chloride, sodium lactate, and large amounts of fluid, persistent control of the signs and symptoms of insufficiency was achieved only after a relatively enormous dosage of desoxyeorticosterone acetate was additionally given. Once the insufficiency had been controlled, much smaller doses of all the therapeutic agents were effective. At one point in the course of treatment of this patient when both desoxyeorticosterone acetate and adrenal cortical extract were being given, decreasing the amount of adrenal cortical extract from 20 ml. to none had little if any discernible effect, whereas during a subsequent period when he was receiving no adrenal cortical extract, decreasing the dosage of desoxyeorticosterone acetate from 2 mg. to none and even from 2 mg. to 1 mg. produced a striking change. We cannot, however, assay the relative potency of the two compounds in controlling water and electrolytes in this patient from these observations since adrenal cortical extract was probably being given in excess of the patient's needs when it was decreased, whereas when the dosage of desoxyeorticosterone was decreased he was close to his minimal requirements for exogenous electrolyte and water controlling hormone. At no time during the period when he was receiving

such enormous dosages of desoxycorticosterone acetate did he show roentgenographic evidence of cardiac enlargement or clinical edema which would suggest overdosage of the hormone. At the present time, at the age of 4 months, the patient seems to be well controlled on the regimen described, which consists of a regular infant diet with 3.5 Gm. of sodium chloride and 0.8 Gm. of sodium lactate added to the formula and the daily intramuscular injection of 2 mg. desoxycorticosterone acetate in oil. From Darrow's observations,<sup>6</sup> we have considered the advisability of including the addition of potassium chloride to this regimen. However, from data derived from detailed observations on his electrolyte balances with varying intakes of sodium chloride, and potassium, which are reserved for later publication, it appears that he does not need potassium in excess of the amount he is receiving in his milk.

DR. LEVINE.—Would you be willing to venture an opinion as to the prognosis, Dr. Barnett?

DR. BARNETT.—The number of cases in which this abnormality has been diagnosed before death and in whom follow-up observations were made is so small and the progress of the few who have been followed varies so greatly that no reliable prediction concerning this patient's future is possible. From what we do know, the prognosis is not very hopeful. The patient described by Butler, Ross, and Talbot<sup>8</sup> in 1939 is still alive at the age of 11 years and shows persistence of his water and electrolyte disturbance, deep pigmentation, extreme virilism, and dwarfing. Thelander's patient<sup>9</sup> died at 6 years with measles. His need for hormone had also persisted and extrapolation of his rate of growth suggested that his ultimate height would have been below average. The poor response to infections suggested in this patient has been apparent in others. Darrow's patient<sup>10</sup> died at about the age of 4 years and showed diffuse enlargement of the adrenals and an enlarged heart. The patient reported by Wilkins, Fleischmann, and Howard<sup>3</sup> died at  $3\frac{1}{2}$  years of age when an excess salt intake was inadvertently interrupted.

VISITING DOCTOR.—May I ask Dr. Barnett about the effect of this severe metabolic disorder on mental growth? It has been stated that at present the patient's mental age is normal or above. If he survives, what is his prognosis in this respect?

DR. BARNETT.—The children reported by Butler, by Darrow, and by Wilkins showed definite evidence of mental retardation. Thelander's patient, on the other hand, exhibited normal mental development, and with psychiatric help and through an intelligent attitude of everyone concerned, including not only the parents but neighbors, nursery school teachers, and others, he did very well in his emotional adjustment.

The difficult emotional adjustment which confronts this patient and his family presents a problem of equal magnitude to that posed by his metabolic difficulties. The problem has been approached initially by the pediatrician, taking advantage of the relationship which has already been established. An attempt is being made to help the parents to accept first intellectually and then

emotionally the baby's differences from other children. Since his differences will be primarily sexual manifestations, their own attitude toward sex must be examined in order for them to face realistically their emotional reaction to the child. At a later time the family may need the help of a fully trained psychiatrist, and the present role of the pediatrician is to prepare them for this. The question of future pregnancies has been discussed and the occurrence of similar disorders in siblings described. This was done after considerable preparation and did not appear to be too immediately disturbing. No pregnancies are contemplated for the next year or two, during which time there will be opportunity for further discussion.

DR. LEVINE.—It seems clear at the present time that there are at least three distinct functions of the hormones of the adrenal cortex. Desoxycorticosterone acetate is at least one of the hormones which controls water and electrolyte excretion, and we have adequate evidence of such insufficiency in this patient. The 17-ketosteroids are among the hormones responsible for the development of some of the secondary sexual characteristics, and the increased urinary excretion of this hormone in the urine and the clinical suggestions of beginning virilism are strong evidence for an excess of this hormone. Hyperplasia of the androgenic cells may actually be responsible for failure of the other cells to function. Are there any evidences of disturbance in the 11 oxysteroids, which are concerned with sugar-fat-nitrogen metabolism?

DR. BARNETT.—Evidence for sugar-fat-nitrogen hormone deficiency has not been prominent in the reported cases. Our patient's episodes of cyanosis and collapse during the first month of life could have been due to hypoglycemia. This suggestion is strengthened by the finding of a blood sugar value of 36 mg. per 100 ml. here. However, there have been no further evidences of disturbance in this area, so that it seems likely that either he has none or that it is of such a slight degree that regular feedings would be sufficient to prevent periods of hypoglycemia. I would suspect that he might not tolerate prolonged periods of fasting well.

VISITING DOCTOR.—Were there changes in blood pressure during the periods of varying control?

DR. BARNETT.—There did not appear to be. There were at least no periods of definite hypotension or hypertension that could be correlated with his changing status.

VISITING DOCTOR.—Is there any possibility of the signs and symptoms of adrenal insufficiency in this infant disappearing so that later he will not require hormone and added salt?

DR. BARNETT.—In the last few years Dr. Jaudon of St. Louis has emphasized a syndrome characterized by nausea, regurgitation, vomiting, eventual dehydration, and collapse, accompanied by excessive renal loss of sodium chloride and water. He attributes the cause of the syndrome to a temporary absence or a physiologic low supply of the electrolyte and water-controlling hormone of the

adrenal glands, and has presented evidence<sup>11</sup> to demonstrate that adrenal cortical hormones and salt are of specific therapeutic value in these infants. In these infants, therapy can eventually be discontinued and there has been no laboratory or clinical evidence of virilism. We have not seen any infants here who we thought belonged in this category and although Jaudon's evidence for the existence of such a syndrome is suggestive, we cannot accept it unqualifiedly. Of the patients who have shown adrenal cortical insufficiency associated with virilism, the need for continued therapy with desoxycorticosterone, salt, or both has persisted in all instances and this is what we must expect, therefore, in this infant.

DR. LEVINE.—We expect to see this patient at frequent intervals and will hope to present him for a follow-up at some future date.

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#### Case 3. Cholelithiasis in Childhood

DR. LEVINE.—The third child on our list today has been discharged. We present her case not as a diagnostic or therapeutic problem, but because it illustrates a surgical condition which is relatively infrequent in childhood.

DR. SARAH MATTESON (Intern in Pediatrics).—B. G., a 5½-year-old white girl of Italian parentage, was admitted to the New York Hospital in December, 1948, with the complaint of recurrent abdominal pain since the age of 3 months. With the introduction of solid foods to the diet, she began to have attacks of abdominal pain associated with nausea and vomiting. Until 3 years of age the episodes occurred once or twice a month. From then until the time of admission to the hospital the attacks became more severe and occurred two to three times a week. Each lasted about two to three hours and was accompanied by nausea and vomiting. The mother stated that the pain seemed to be related to the eating of fatty foods. No jaundice was noted. On a low fat diet the severity and frequency of the attacks diminished. However, the patient repeatedly com-

plained of a dull ache in the abdomen, usually on the right side, which remained more or less constant between the acute episodes. Plain roentgenograms of the abdomen at 4 years of age revealed calcific densities in the right upper quadrant which were interpreted as gallstones.

On admission, the positive physical findings were voluntary spasm and questionable slight tenderness to deep palpation in the right upper quadrant, and a smooth, nontender liver edge palpated 1 cm. below the right costal margin.

Laboratory studies including complete blood examination, liver function tests, and sedimentation rates, revealed no evidences of a hemolytic anemia, infection, or liver disease.

DR. LEVINE.—Before we hear about what was found and done at operation, I shall ask Dr. Dale to present the x-rays (Fig. 4).

DR. JOHN H. DALE, JR. (Assistant Professor of Pediatrics in Radiology).—Oral cholecystography showed a well-filled gall bladder which appeared normal in size, shape, and position. There were two calcific densities in the fundal region and another ovoid density in the region of the cystic duct. Examination of the gastrointestinal tract revealed an elongated, narrowed, pyloric canal with evidences of retention of the barium meal. The duodenal swing was wider than usual. It was thought that there was moderate pylorospasm and possibly enlarged lymph nodes in the region of the head of the pancreas accounting for the widened duodenal loop.

DR. LEVINE.—Does anyone have any questions before Dr. Matteson goes on with the description of the operation and subsequent course?

DR. MATTESON.—At operation, the gall bladder was exposed and found to be thickened and edematous but not inflamed. The gall bladder was adherent to the second portion of the duodenum, accounting for the widened duodenal swing. The structures within the loop of the duodenum were normal. External examination of the gall bladder failed to reveal any evidence of a cystic duct. On opening the organ, two green stones were found in the fundus. The cystic duct seemed to be almost lacking and was represented by a few mucosal folds simulating the valves of Heister. Caught within these folds was a long, spiral-shaped gallstone. The gall bladder appeared to unite directly with the common duct. No calculi were found in the latter. The gall bladder was removed. The pathology report was "chronic cholecystitis with cholelithiasis."

Recovery was uneventful and the child was discharged ten days after operation. Follow-up during the past two months has revealed a complete freedom from all previous symptoms.

DR. LEVINE.—I am sorry we do not have this patient here, but when last seen she showed no positive findings except for her healed abdominal incision. The liver was not enlarged. I will call on Dr. Dale to discuss cholecystitis and cholelithiasis in childhood.

DR. DALE.—Gall bladder disease in childhood has been considered to be rare. The diagnosis is seldom entertained and many cases are diagnosed only at the

time of operation for some other intra-abdominal condition or at autopsy. In 1938, Potter reported a total of 432 cases of gall bladder disease in children collected from his material and from the literature. Of these, 306, or approximately 70 per cent, had cholelithiasis. Ladd and Gross state that cholelithiasis is far more common in childhood than acute cholecystitis.

The symptoms are similar to those noted in adults but are less well localized. Referral of pain to the shoulder or the back is not the rule in children. The chief symptoms are periumbilical or right upper quadrant pain associated with



FIG. 4.—A, Oral cholecystography demonstrating the presence of gallstones and the stone in the cystic duct. B and C, Preoperative and postoperative changes related to the pylorospasm, and widened jejunum of the duodenum, shown at operation to be secondary to adhesions between the gall bladder and the duodenum.



nausea and vomiting. There is usually fever. Physical examination may reveal tenderness in the right upper quadrant associated with spasm. Occasionally the distended gall bladder may be palpated below the right costal margin. In young children the condition is usually diagnosed as acute appendicitis. The diagnosis of gall bladder disease in childhood is best made by oral cholecystography.

Most authors are in agreement that the majority of cases of gall bladder disease in children are attributable to congenital anomalies of the biliary system, systemic infection, upper respiratory infection, infection of the gastrointestinal tract, or to parasitic infestation. The fact that the incidence of gall bladder disease has not decreased with the lowering of the incidence of typhoid fever suggests that there has been overemphasis of the importance of the latter in the production of gall bladder disease. Cholelithiasis is frequently associated with the congenital hemolytic anemias. In fact, the presence of gallstones should alert the clinician to the possibility of the existence of one of this group of anemias. Cholelithiasis may result from biliary stasis secondary to malformation of the extrahepatic biliary system, from infection of the gall bladder, spasm of the ampulla of Vater, extrinsic pressure of enlarged lymph nodes on the common duct, or from inflammation of the common duct. In this case, it would seem probable that the malformation of the cystic duct was the responsible factor in the production of the infection and the gallstones.

The treatment of choice is operative. If there is no evidence of infection, as is the case in the hemolytic anemias, the stones may be removed and the organ left in place. If infection is present, cholecystectomy is the operation of choice.

VISITING DOCTOR.—Was there anything unusual about the composition of the stones?

DR. DALE.—The gallstones removed in this case were composed chiefly of bilirubin, the most common type of stone found in gall bladder disease in childhood.

# Psychologic Aspects of Pediatrics

## PSYCHOSOMATIC ILLNESS IN CHILDHOOD

### A REPORT OF SIX CASES

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PSYCHOSOMATIC illness mimics so closely the symptoms of organic disease that its recognition as a clinical entity is an important advance of modern physical diagnosis. Case reports for the most part have emphasized psychosomatic illness in the adult. Recent statistics compiled at the Lahey Clinic<sup>1</sup> showed that in 27 per cent of 1,000 consecutive adult medical admissions complaints were of nervous and mental origin only. In another 13 per cent of these patients organic and functional symptoms were combined. Such reports have prompted us to examine our pediatric records.

A new awareness of functional disorders is demonstrated in the medical service of the Children's Hospital of Pittsburgh. In 1941 the diagnosis of "psychosomatic illness" was made in only twenty-eight cases of 2,068 medical admissions. However, during the past six months, from an admission census of 1,328 patients, our medical records describe twenty-four cases of uncomplicated psychosomatic disease in children. These statistics do not imply a new trend in childhood illness but rather indicate a change in our evaluation of the pediatric patient.<sup>2</sup>

### EVOLUTION OF PEDIATRIC PSYCHIATRY

It is not a purpose of this paper to trace the growth and development of pediatric psychiatry. This has been described elsewhere by Kanner,<sup>3</sup> who has reviewed in detail the evolution of child mental health programs. Today certain factors still complicate the approach to psychosomatic illness in the child. For example, the acceptance of such a diagnosis as behavior problem is difficult for parent and physician alike. Arriving at this diagnosis by the usual methods of exclusion of organic disease is expensive. Correction of the inorganic complaints, employing the crude techniques at our command, may be tedious and at times quite unsatisfactory. These difficulties constitute the growing pains of pediatric psychiatry.

### APPROACH TO THE EMOTIONALLY DISTURBED CHILD

To the clinician, paradoxically, failure to recognize organic disease seems a far more serious oversight than neglect of a behavior problem. Why should this be? There are certain fundamental emotional demands in this age period.

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No description, however graphic, portrays so well the innermost emotions of a group as does the child who mirrors without distortion all conflicts within the family. Reflected in the emotional outlook of the pediatric patient is an image of the good or bad home environment.

Primary causes of misbehavior include personality oversensitivity, conflicts with home influences, problems of growth and development, pressure of education, and the frustration of instinctive drives.<sup>4</sup> Some combination of these often represents the uncertainties which bring the functionally imbalanced child to the physician.

#### NOMENCLATURE AND DIAGNOSIS

We have preferred to leave the distinct classification of our cases to the psychiatric consultant. The Committee on Statistics of the American Psychiatric Association has classified the usual psychoneuroses into six separate types: hysteria, psychasthenia, hypochondriasis, anxiety state, neurasthenia, reactive depression (a simple situational reaction), and a mixed group. These diagnoses are readily applicable to the cases presented below. Diagnostic techniques may be simplified also. The first step is elimination of all possible organic foci of disease. Next an evaluation of emotional influences is necessary. Finally there is formed a diagnosis which classifies the etiology of the illness rather than the child.

#### DIRECT AND INDIRECT THERAPY

The clinician who follows a scheme of systematic analysis should be able himself to evaluate, diagnose, and initiate therapy in the majority of cases. Adjustment of the child rather than mere elimination of symptoms is his primary aim.<sup>5</sup> With the family he approaches directly the genesis of the child's behavior problem. The community provides the indirect social, economic, and religious agents necessary for readjustment of distorted family relationships. Where the psychoneurosis is of serious consequence or where organic mental illness is a factor, only the child psychiatrist is equipped to direct patient guidance. For these refractory cases clinics affording specialized therapy are available.<sup>6</sup>

#### CASE PRESENTATIONS

We present five cases selected from among fourteen children, diagnosed as uncomplicated psychosomatic problems, admitted to the medical service of Children's Hospital of Pittsburgh between May and September, 1948. The sixth case presented is taken from our outpatient department records during this period. These patients range in age from 2 to 13 years. Each illustrates bizarre behavior patterns which are characteristic of childhood psychosomatic illness.<sup>7</sup>

CASE 1.—The first case is described in some detail to illustrate its far-reaching ramifications of social, economic, and religious significance.

L. W., a 10-year-old white girl, was admitted July 29, 1948, with a chief complaint of daily attacks of sharp, substernal pain lasting one-half to two hours.

*Past Medical History.*—The mother stated the child had been "sensitive" since birth. A 2-month premature infant weighing 5 pounds at birth, L. had "practically lived on whiskey" for the first five months of her life. The child began to speak at 12 months and walked at 17 months. The past medical history was negative for acute infectious or chronic disease. From July 20 to July 27, 1948, the child had been a patient at a local hospital where only a few attacks had been modified by phenobarbital sedation. Because she was "an unmanageable neurotic" she was discharged.

*Family History.*—The father, aged 32 years, was a hard-drinking coal miner in good health. The mother, aged 28 years, described herself as "nervous." She suffered frequent palpitations of the heart and complained of chronic fatigue. There was no history in the family of mental disease or chronic illness.

*Present Illness.*—The attacks began one month prior to admission; they were manifested by substernal pains of crushing nature which the patient stated "cut off my breath."<sup>8</sup> Such attacks, occurring between 7 P.M. and 1 A.M., had been noted on all but six nights in the past month, lasted from one-half to two hours, and left the child completely exhausted. During an attack the mother would hold the child, who was extremely emotionally upset, and often would cry with her, advising her "to scream and get the poison out of her system." As the outbursts became more prolonged the child would gag and vomit mucus; the mother would then give her small amounts of whiskey, which partially relieved her. Following a typical attack the child would fall into a deep sleep.

Such episodes occurred always in the absence of the patient's father, either while he was working on the night shift or out "at the club." The child could foretell an attack a few minutes before its onset; she had never bitten her tongue or been incontinent in an attack.

*Physical Examination.*—The patient was asthenic, pale, and tense; she did not appear acutely ill. Physical examination was negative except for a generalized hyperreflexia and a nervous tenseness of the abdominal wall on palpation.

*Laboratory Studies.*—X-rays of the chest and gastrointestinal tract, as well as cholecystogram, electrocardiogram, electroencephalogram, and pneumoencephalogram were essentially normal. Routine urinalysis, complete blood count and sedimentation rate, serology, and spinal fluid examinations were all reported normal.

*Course in the Hospital.*—A fat-free diet was prescribed for the child at the time of her admission. Psychiatric interviews were arranged.

*Attacks in the Hospital.*—During the first week of hospitalization the child had nightly seizures of which the following, a description of the attack occurring at 7 P.M. on the day of admission, is typical:

The patient first began to complain loudly of left-sided chest pain. When seen by the house physician she was clasping her heart and rocking back and forth in bed, moaning loudly. After a few minutes she began to gag and

choke, spitting up a considerable quantity of frothy mucus. Examination disclosed her blood pressure during the attack to be 78/56; normal sounds were auscultated over the heart. The apical rate was 88 per minute. Peristalsis was normal and there was no muscle splinting over the abdomen. The chest was clear to auscultation. There was no tenderness elicited on pressure over the xiphoid process nor did pressure on the ribs modify the pain.

The patient had had a slice of toast and a glass of skimmed milk immediately preceding the attack but did not vomit stomach contents. At one time during the attack she requested whiskey "which helped me at home." The attack was relieved by a hypodermic of sodium phenobarbital and the patient dropped off into a deep sleep.

*Therapy.*—During the first week attacks were controlled by sedatives, while the child was evaluated clinically and organic disease ruled out as carefully as possible by the tests described above. Mild suggestion to the patient that some relief might follow the x-ray studies did not alter the pattern of her attack.<sup>9</sup>

After completion of the negative studies, psychotherapy was begun. At first L. was told that she would not be sent home until her attacks had ceased. Rapport was established after several interviews and aeration of her views on home conflicts was encouraged. After she had been reassured that family troubles would be cleared up her personality changed; she became cheerful, alert, and helpful. She was rewarded for improvement by assignment as helper in caring for a few of the younger patients on the ward. She responded well to this treatment and remained free of attacks from Aug. 7, 1948, until her discharge on August 12.

*Social Service Investigation of the Patient.*—The patient had good relationships with teachers, friends, and neighbors, as well as her sisters. She had always been shy and reticent and her intelligence was estimated to be above normal for her age.

*First Social Service Interview With Mother.*—During the interview the mother manifested many nervous complaints and stated that she often felt ill and nauseated "just like L." The mother described the father as drunk and abusive to her and to the children. He gambled heavily and they had quarreled frequently. Although in the past he had seldom struck the children, he often threatened to choke them "if they didn't keep quiet." However during the week prior to L.'s admission, the father had beaten the younger son (aged 8) several times. The boy had run away from home on two of these occasions and the mother said he, too, was a problem child.

The mother stated the patient seemed to fear the dark, to fear storms and loud explosions, and to fear that the father would choke her mother or herself.<sup>10</sup> She frequently lay awake at night asking repeatedly whether her father would come home drunk. The mother stated that she was unable to divorce the father because of their religious belief, but she only "tolerated him for the sake of the children."

*Social Service Interview With Father.*—Although evasive in his answers early in the interview, the father at length stated that perhaps several quarrels with his wife in the presence of the patient had made the child nervous. He said he had never touched L., but had once or twice threatened her. He confessed that he had drunk and gambled during the early years of his marriage, but in the past two years, realizing his family life was insecure and the home atmosphere was bad for the children, he had tried to stay sober and stop squandering money. He felt that his wife would not forgive him for past grievances, and would not help him in the attempt to create a good family life. For three months she had refused to sleep with him, and occasionally she would not speak to him for several days at a time.

At the conclusion of the interview it was suggested to the father that the mother and children were fearful of abuse and were frightened by lack of security in the home. With this simple explanation as the probable source of the child's illness the father agreed to cooperate in changing the family atmosphere, to show concern for his wife's poor health, and to discipline his own habits.

*Second Social Service Interview With Mother.*—During the second interview the mother was encouraged to be more tolerant of the father in his attempt to reform, to forget past grievances, and to seek encouragement from the local social service counsellor, who was given a summary of this case. She was reassured about the prognosis of the illness of her problem children. She was also offered the service of a medical clinic for evaluation and treatment of her personal health problem. Finally, she was urged to seek the advice of the local priest whom she trusted and had known since childhood.

*Disposition of the Case.*—The social service worker in this family's community was given responsibility for rehabilitation of the patient and her family. It was her report on family conditions, undertaken at the referring physician's request, which had focused attention on important environmental factors in the case.

The referring physician was sent a detailed summary of the case. He assumed responsibility for medical care of the family.

The local priest, who showed great interest in the case, undertook the program of spiritual guidance which has ultimately proved most efficacious in resolving many of the parents' differences.

**CASE 2.**—Our second case, seen in the outpatient department of the Children's Hospital in September, 1948, illustrates still another type of psychosomatic problem. In this instance a chance remark of the parent led to the uncovering of a whole series of difficult family conflicts.

L. M., a 5-year-old white girl, was examined on Sept. 19, 1948. Her chief complaint was anorexia and vague abdominal pain, and sore throat of twenty-four hours' duration. Past medical history was essentially negative.

*Family History.*—The mother, father, and a sibling aged 15 months were all living and well. There was no family history of chronic disease. The mother, aged 24, was a college graduate. The father, aged 30, was an office clerk with a high school education.

*Present Illness.*—During the past month the child had manifested anorexia with slight, generalized abdominal pain occurring always during or immediately following the evening meal.<sup>11</sup> These symptoms became aggravated at the child's bedtime, and she often stayed awake demanding sympathy until her father had gone out for the evening. The child would fall asleep after his departure. She had never vomited or gagged, but showed her discomfort by groaning and whimpering aloud. Her bowel movements were regular and she had no urinary complaints. She had developed a mild upper respiratory infection one day prior to her visit to the clinic; this was the primary concern of the mother.

*Physical Examination.*—The patient was intelligent, talkative, well developed and well nourished; she did not appear acutely ill. Positive physical findings included a nasopharyngitis and a few excoriated areas about the labia and rectum.

*Additional Information.*—Because of the peculiar pattern of the above complaints, the mother was questioned more closely when the physician had finished his physical examination of the child. The parent stated that she believed the patient resented any affection of the father for the mother or the patient's sibling. The child would greet the father as he returned from work just before supper with the announcement, "I've been sick all day." This would provoke him to accuse the mother of neglecting the child and thus set the stage for several family arguments in the course of an evening. L.'s symptoms of anorexia and abdominal pain would begin if the father did not feed her or hold her on his lap during the evening meal. These complaints were aggravated by any attention the father might give the mother or sister during the remainder of the evening.

The mother said that since the birth of her younger child the husband usually went out every evening, sometimes not returning home at all. She confided that she and her husband had not been sleeping together since her last pregnancy. She added that when the father did sleep at home, the patient would insist upon sleeping with her mother. The mother commented that she felt all this was because the child "knew too much" and "was jealous" of her mother, as well as her sister. She said her husband accused her of not loving L. as well as her sister, and was flattered by the child's demonstrations of affection. As a result, he neglected the younger sister.

The patient was given a prescription for her cold and the mother was admonished to return with the child to the Neurology (Behavior) Clinic the next morning.

*Social Service Follow-Up.*—The mother failed to keep the appointment at the Behavior Clinic. A social service worker was asked to interview the family. The mother was telephoned but was unable to make an appointment for an interview at the hospital. She reluctantly agreed to a home visit by the social worker.

*First Social Service Interview With Mother.*—The mother said the family had moved to Pittsburgh twenty months previously, but had not made any new acquaintances. She eagerly confided that the patient was a masturbator; she had noted this first when she had returned from the hospital with the new

baby. L. was described by the mother as rubbing her thighs and genital areas to stimulate herself, working up a perspiration and seeming to achieve climax.<sup>12</sup> The child had told the mother she had seen her aunt doing this. The aunt had cared for the patient while the mother was at the hospital.

Prior to the time the mother had gone to the hospital the child had slept in the same room with her mother and father. When in the fifth month of her second pregnancy the obstetrician had restricted the mother's sexual activity, the father had suggested the mother and L. sleep together in a bedroom separate from him. During the past fifteen months the mother had been unable to change this arrangement. The baby slept alone in a crib in another bedroom, for L. refused to sleep on the cot provided for her there.

The social worker observed that the 15-month-old sister was obviously her mother's favorite.<sup>13</sup> All play centered about the baby, and if the patient tried to play with her sister's toys, she was immediately disciplined by her mother. This would provoke a stormy family scene.

*Second Social Service Interview With Mother.*—A second home interview was held on Sept. 23, 1948. At this time the mother questioned whether she might regain her husband's attention by taking a position in the office with him, leaving the children in the care of a nursemaid. It was pointed out to the mother that her duty was gradually to break L.'s habit of sleeping in her bed, and to turn her attention from sexual abuse. The mother was horrified at the suggestion that she might take the first step toward renewing relations with her husband. The social worker attempted to persuade her to seek advice from the local Child Guidance Center. Despite frequent follow-up attempts by the social agencies and the center the mother continued to disregard the problems of her child, refusing further interviews or counsel and stating she was "sorry she had ever begun this business."

*Disposition of the Case.*—Unfortunately, we have as yet no means of enforcing our prescription for psychotherapy in cases such as the above. The unsatisfactory disposition of the case illustrates well the resistance of a modern family to even the most tactful attempts at psychiatric guidance. Such an attitude constitutes a very real obstacle in pediatric psychiatry today.

CASE 3.—This case demonstrates thorough study of a typical behavior problem.<sup>14</sup>

F. H., a 28-month-old white female child, was admitted Aug. 30, 1948, with a chief complaint of temper tantrums and hyperactivity of two months' duration.

*Past Medical History.*—This disclosed a normal birth and developmental background. The patient had been painstakingly trained in her bowel habits by the age of 10 months. There was no history of acute infection or chronic disease.

*Family History.*—There were no siblings. The mother, aged 27, had had two years' training as a nurse; she complained of bad nerves. The father, a pharmacist aged 28 years, was in good health. There was no history of organic familial disease.



*History of the Patient's Illness.*—The patient had always been restless and unmanageable, but the mother had noted a decided change for the worse in the child's conduct during the past two months. At this time the family had moved into a new two-story apartment and F. had refused to sleep in her new room or bed on the second floor. The child insisted instead that she sleep downstairs on the couch near her parents. She often picked up dirt, cigarettes, or grass and ate them, even though she was spanked severely for such actions. When spanked she became completely wild; when confined to her room for punishment she would scream at the top of her lungs, often for as long as one or two full hours.<sup>20</sup>

*Physical Examination.*—The patient was well developed and well nourished, uncooperative and irritable; she resisted the examination with screams and several times attempted to bite the examiner. There were no unusual physical findings. A thorough neurological examination revealed no abnormalities.

*Laboratory Studies.*—Blood and urine studies, serologic examination, sedimentation rate, and chest x-ray were all reported as essentially normal. Studies for heavy metal poisoning were negative. Therapeutic vitamin therapy with moderate sedation had little effect upon the tantrums. Two psychometric tests (Cattrell and Merrill-Palmer) given at this time showed the child to have a mental age of about 22 months, interpreted by the psychologist to reflect neglect of the patient's abilities by her parents.

*Course in the Hospital.*—Because parental visits precipitated loud outbursts, the family was requested not to visit the child. The mother retaliated by having the child moved to a private room where she might exercise unlimited visiting privileges. Despite large doses of phenobarbital and reassurance by the nurses, F. was completely unmanageable, passing from one tantrum to another whenever she was left alone. These outbursts were characterized by crying, lusty screams, and sustained physical activity.

Finally on Sept. 3, 1948, her parents were prevailed upon to return the child to a ward with children of her own age. By September 7 the patient was much improved. She had had no further tantrums and was responding well to the affection of the nursing staff. She had begun to play with her fellow patients and demonstrated an alert mind and pleasing temperament.

At the time of her return to the care of the referring physician on Sept. 21, 1948, the patient had changed completely in personality and exhibited no further emotional displays. Her mother was reassured and given counsel during weekly visits to the pediatrician. In an interview on Dec. 21, 1948, the parents said both they and the child had profited by the family physician's advice and were much happier. There had been no recurrence of F.'s temper outbursts.

*Social Service Interview With Mother.*—The mother was an exceedingly well-groomed and comely woman who was very conscious of her economic independence. She stated that she had been greatly upset two years previously by the death of her mother, upon whom she had been wholly dependent for love, security, and advice. Following the death of her father one year previously, she had begun to feel "terribly alone and insecure." She related that

oftentimes her nervous energy became so great that she would stand in the middle of the floor and scream and cry at the top of her lungs—all actions which the child, when frightened, would imitate.

*Second Social Service Interview With Mother.*—The mother felt that on her husband's return from service he had attempted to understand her nervousness and frigidity, but lately he had begun to stay out late and to ignore his wife except when criticizing her. He had arranged the new apartment so that he and his wife slept in twin beds. Recently he had become demanding, short-tempered, and had told his wife on several occasions that she "was spoiled and needed a good spanking like F." In the past two months he had retaliated, whenever the patient threw a tantrum in his presence, with a severe spanking. When annoyed by the child, he disciplined her by sending her to bed without supper or shutting her in a darkened room, advising her to "cry all she wanted to."<sup>15</sup>

*Disposition of Case.*—A program of de-emphasis of the mother's home activity and an opportunity for her to study interior decoration, home planning, and engage in community activity was arranged. The child was provided with nursery facilities under supervision of a trained psychologist. The parents were referred to their family physician who was able to adjust the parents' emotional misunderstanding and their mismanagement of the child.

**CASE 4.**—This case presents a slightly different approach and is included to illustrate the advantages when therapy of the patient is conducted in a convalescent home. Such facilities usually place an increased economic demand upon the parents. However, where symptoms persist and where the etiology of the illness remains obscure, this type of therapy has proved most successful.<sup>16</sup>

J. C., a 13-year-old Italian youth, was admitted Aug. 25, 1948, with a chief complaint of nervousness and vomiting associated with weight loss during the three weeks prior to admission to the hospital.

*Past Medical History.*—The parents described a normal birth and developmental history for this boy. There was no history of acute or chronic diseases.

*Present Illness.*—On Aug. 14, 1948, the patient had been a camper at a summer cabin with a group of eight boys his own age under supervision of a YMCA leader. J. had been free of symptoms before he left home, but after two days at camp he was sent home because he complained of anorexia and nausea with postprandial vomiting.<sup>17</sup> The patient stated that food at the camp was greasy and seemed "to stick in his throat." He just couldn't swallow it and when he had eaten a small amount of this food he would gag and vomit. During the ten days preceding his admission to the hospital he moped about the house, refused to eat at all, and cried when anyone tried to question him about his illness. He had no dysphagia, hematemesis, or dysarthria. He had lost about ten pounds during the period of fasting.

*Physical Examination.*—The patient appeared pale and asthenic, but was not acutely ill. He answered questions in a low voice, was easily upset, and

refused to look directly at the examiner. The examination was negative except for the patient's obviously weakened condition. A thorough neurologic examination was normal.

*Laboratory Examination.*—X-rays of the chest, gall bladder and gastrointestinal tract disclosed normally functioning organs. Blood, urine, and serologic studies were normal. Gastric drainage showed normal concentrations of free and combined acid.

*Social Service Interview With Parents.*—The parents believed the home life of the patient was a happy one; his siblings were free of nervous habits. However, the patient was described as always having been sensitive, quick to cry when his feelings were injured, and retiring among his playmates. He found school work difficult but with effort managed to maintain a "C" average.

The mother stated that since his return from camp he had refused to eat even specially prepared dishes of which he was very fond. He had had violent nightmares during which he tossed and turned restlessly, occasionally waking himself by crying out in his sleep. He told his mother that he had been picked on at camp. The other boys had warned him of bad men who would dope his food and then carry him away while he slept. J. had been afraid to eat, and even at home had told his mother "he knew the bad men would find him."<sup>18</sup>

*Course in the Hospital.*—The patient refused to eat solid or semisolid foods during the first three days of his hospitalization. Mild sedation produced no improvement and he continued to manifest profound nausea at the sight or odor of all food. On the first day gastric studies were done and the patient was given gavage feedings for twenty-four hours to accustom the shrunken, fasting stomach to food. J. protested, but retained all of these feedings.<sup>19</sup>

With assurance that forced feedings would cease only after he had begun eating of his own accord, J. took his first oral semisolid feedings on the fourth hospital day. With firm but kindly nursing care he had developed tolerance for the full house diet by the eighth day. Although the patient was more cheerful now, mention of home or camp or visits from his family would cause him to become nauseated and vomit even at this stage of convalescence.<sup>20</sup> Nevertheless, he was homesick.

Neither the house staff nor the neurological or psychiatric consultants were able to establish rapport with the patient to learn firsthand the incidents that had produced such a deep-seated anxiety. Because of the obscurity of these causes, and because of the patient's slow improvement while in the hospital, he was transferred out of the city to the convalescent ward on Sept. 10, 1948. After two days of recurrence of nausea and vomiting, J. gradually resumed eating and later began to play with the other children in the ward. However, a month elapsed before the weekly visits of his family ceased to upset him. At the time of his discharge to his family the patient had gained twelve pounds and was free of depression.

*Disposition of Case:* The patient visited Child Guidance Clinic for an interview on Dec. 18, 1948. At this time the social worker in charge of his case noted that J. was apparently the normal happy child he had been before the experiences of his camping trip in July had frightened him.

CASE 5.—The last two cases are typical of those most responsive to treatment by the family physician.

H. G., a 4-year-old white female child, was admitted Sept. 26, 1948, with a chief complaint of faulty eating habits associated with weight loss, increasing during the past six months.

*Past Medical History.*—The child had been born and had developed normally; no history of previous infectious or chronic diseases was given.

*Family History.*—There was one sibling, aged 3 weeks, living and well. The father, a draftsman aged 30 years, manifested an allergy for many foods and exercised constant care in the choice of his diet. He was also very limited in his food likes. The mother, aged 28, a college graduate, had been very nervous and easily upset since the birth of the patient.

*Present Illness.*—Since infancy the patient had been a poor eater. Up until she was 12 months of age she had eaten well only with coaxing and bribing. However, during the six months prior to admission, the patient had mimicked her father's intolerance for many foods, including bread and milk. She had no regard for her mother's attempts at discipline and the mother stated "she simply hadn't the heart" to be stern with the child.

Since the mother's duties as dietitian necessitated catering to the whims of both her husband and child, she had become very temperamental, for she disliked cooking. The father, for this reason, became aggravated and would fly into a rage when the mother would mention her difficulties in planning the daily menu. During such outbursts the parents would argue as to whose fault it was that the child was ever born, and even criticize one another's poor taste as reflected in the child's appearance and her dress. Such discussions visibly upset the child and the mother said that H. would leave the table and shut herself in her room to sulk and cry. Since these arguments occurred most frequently at mealtime, the mother "wondered why the child ever ate anything any more."

*Physical Examination.*—The child was well developed, well nourished, and intelligent. There were no abnormal physical findings.

*Laboratory Examination.*—X-rays of the chest and gastrointestinal tract, together with complete blood count, urinalysis, sedimentation rate, and tuberculin test, were essentially negative.

*Course in the Hospital.*—Within twenty-four hours after admission the child was eating hungrily all food on her hospital tray. She was alert, happy, and active in group play. However, visits by the parents would depress the patient and cause her to lose her appetite for a short time.

*Disposition of the Case.*—The patient was discharged to the care of her grandmother for a two-week vacation while the referring practitioner undertook management of the family emotional problems.<sup>21</sup>

CASE 6.—C. P., a 12½-year-old white girl, was admitted May 5, 1948. The chief complaint was pain in the left chest of thirty-six hours' duration.

*Past Medical History.*—This child had had an appendectomy at Children's Hospital on April 2, 1948. She had an uneventful convalescence and was apparently well until the present admission. Otherwise the past medical history was negative.

*Family History.*—The mother and two siblings were living and well. There was no history of epidemic or chronic disease in the family.

*Present Illness.*—Thirty-six hours prior to admission the patient had suffered a sudden shaking chill followed by sharp substernal pain which had persisted in the left anterior and lateral chest.<sup>22</sup> The child complained that this pain would increase when she took a deep breath. She had no cough or fever on admission, although the mother stated that, following a chill twenty-four hours before admission, the child felt "as hot as if she had a temperature of 104 to 105°." The patient had been treated at home with penicillin and sulfa by the family physician without relief of her pain.

Eight months prior to her admission this patient's father had died of a heart attack. The attack occurred after dinner in the family living room in the presence of the entire family. The patient, always a sensitive child, had been greatly upset. Since this time she had been nervous and had been sleeping poorly.

The present attack of substernal pain occurred following C.'s return from the funeral services held for her high school principal. The child had returned from the funeral apparently in a state of emotional shock and the attack of chest pain occurred in the living room of her home following dinner. The mother stated that C. had been accustomed to seek the school principal's advice in her personal problems ever since her father's death. Upon investigation it was learned that the patient was aware that the school principal had also died of a heart attack.<sup>23</sup>

*Physical Examination.*—The patient was asthenic and apprehensive; she appeared acutely ill with rapid, irregular respirations. In addition to the complaint of chest pain she stated that her abdomen ached. The child stared at the ceiling during the examination and was vague in her response to questions. Neurological examination disclosed a marked hyperreflexia of the extremities and a tenseness of the abdominal musculature.

*Laboratory.*—Electrocardiogram and x-ray of the chest together with blood and urine examinations were reported negative.

*Course in the Hospital.*—While asleep the patient was observed to breathe deeply and regularly. Treatment with mild sedation and bed rest brought prompt recovery from the attack. Her angina-like pain disappeared on the second day. With simple reassurance and kindness the child forgot her symptoms and seemed bright and alert at the time of discharge on the sixth hospital day.

#### SUMMARY

1. Physicians today are more cognizant of psychosomatic illness in childhood.

2. This is evident at Children's Hospital of Pittsburgh, where the incidence of functional disorders has doubled since 1941.

3. Six cases are presented to illustrate the several manifestations of psychosomatic disorders in pediatrics.

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## Comments on Current Literature

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### THE SURGICAL TREATMENT OF MITRAL STENOSIS

A RECENT issue of the *Journal of the American Medical Association* carries an excellent resumé by Dr. B. Noland Carter<sup>1</sup> of the remarkable present-day accomplishments in surgery of the heart and allied great vessels. In discussing cardiac surgery, Carter refers briefly to recent attempts at intracardiac surgery, especially those concerned in the correction of certain types of valvular disease. He emphasizes in conclusion that "it behooves the medical profession in their efforts to reduce the present ravages of heart disease to be aware of what can be accomplished by surgical treatment."

In the April, 1949, issue of *Diseases of the Chest* Dr. Charles P. Bailey<sup>2</sup> discusses the surgical treatment of mitral stenosis. This report is of considerable interest to the medical profession since stenosis of the mitral valve is a comparatively common lesion and a particularly crippling one. Dr. Bailey emphasizes the serious prognosis of mitral stenosis and expresses the belief that there are at least 1,000,000 cases of mitral stenosis in the United States at the present time, one quarter of which are suitable for surgery.

In considering the advisability of attempting surgical relief of mitral stenosis, Bailey points out that pulmonary vascular congestion due to damming-back of blood behind the stenotic valve produces great distention of the left auricle and hypertension of the entire pulmonary vascular bed. While certain operative procedures have been used to relieve the high pressure in the pulmonary veins and left auricle, Bailey contends that this is merely a palliative measure since reduction of pressure in the left auricle would tend to reduce the amount of blood available for the rest of the body. Although the pulmonary signs of mitral stenosis might be improved by such procedures, in his opinion the general condition of the patient might be worsened. He, therefore, advocates direct approach to the problem by correction of the mitral stenotic lesion, employing a procedure which he has called "mitral commissurotomy." He reviews the literature, particularly that reporting experimental work on animals, and points out that regurgitation is undesirable, and may, if the commissurotomy is not done properly, result in aggravation of symptoms.

On the basis of autopsy studies of stenotic mitral valves, Bailey emphasizes that the "plaque of thickened fibrotic tissue is surrounded by a margin of fairly normal valve tissue," and suggests that in an effort to correct the stenosis the stenotic valve may be cut in two by two incisions at the commissures of the valve opening. These incisions should be extended well into the normal valve tissue. If the chordae tendinae remain intact, such an operative result would allow the valve to act more efficiently, and would reduce the tendency to increasing regurgitation. Experience with five patients is reviewed in detail. Four of the five patients died, one apparently as a result of faulty fluid administration. The fifth, however, a 24-year-old white housewife, withstood the procedure very well and seemed greatly benefited by the operation. Seven and one-half months after surgery, the patient is able to do all her own housework, and her ballistocardiographic studies revealed marked improvement in cardiac output on exercise. Physical examination of the heart showed disappearance of the thrill and striking diminution of cardiac murmurs. An added note, dated Feb. 1, 1949, summarizes briefly the results on five additional patients who underwent this operation. Of these two are doing very well.

The discussion of this paper\* merits attention. Dr. Evarts Graham, who was one of the pioneers in surgical attempts to cut the mitral valve, expressed enthusiasm at seeing the beautiful result obtained in the patient presented at the meeting, but cautioned that final judgment must be postponed for a year at least, since these valves which are cut have a tendency to grow together again. He also expressed the desire that physicians exercise care in the selection of patients for operative intervention, that suitable candidates for surgery be provided who are in fairly good physical condition, at least, since intracardiac surgery would have a greater chance of successful outcome if the patients offered a better operative risk at the outset.

During the general discussion Dr. Gordon Murray of Toronto, Canada, referred briefly to his own remarkable results. He explained that his procedure consists in a removal of one cusp of the valve and in a substitution in its place of a new valve constructed from a section of the cephalic vein and a segment of the palmaris longus tendon. Dr. Murray relates that by this operative procedure a valve cusp is reconstructed which seems to work satisfactorily.

Dr. Horace G. Smithy of Charleston, S. C., described experiments in which he was able to demonstrate that a 2 per cent solution of procaine infiltrated into the myocardium prevents the arrhythmias which have been difficult to control during cardiac surgery involving incision of the myocardium. Dr. Graham pointed out that the use of procaine in this manner may be of inestimable value in all cardiac surgery.

With the rapid improvement in anesthesia and general technique in surgical procedures involving the heart and great vessels, it seems possible that even more remarkable surgical correction of damaged hearts will be accomplished. The conception that patients crippled with mitral stenosis might be helped by surgical intervention is very encouraging. In the field of pediatrics, where rheumatic fever and its crippling effects on the heart are prominent phases, the possibility of actual surgical relief when mitral stenosis occurs is of more than academic interest.

If good results are to be expected with this form of intracardiac surgery, patients must be selected with great care, preferably while they are still in reasonably good physical condition. Perhaps surgical correction of mitral stenosis should be advocated in patients of the younger age groups. In any event, decisions concerning such patients require careful consideration and the best available diagnostic help before cardiac surgery is contemplated.

RUSSELL J. BLATTNER.

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\*Dr. Bailey's paper was presented at the Fourteenth Annual Meeting of the American College of Chest Physicians, Chicago, June 20, 1948.



## News and Notes

On April 5 a luncheon was held at the New York Academy of Medicine in honor of Dr. Sidney V. Haas and his completion of fifty years of pediatric practice. A Book of Tribute containing letters from 160 physicians and medical associations was presented to Dr. Haas. Dr. Haas is professor of pediatrics at the New York Polyclinic Medical School and Hospital and pioneered in the use of banana diet in celiac disease and the use of atropine in the treatment of the hypertonic infant.

The Second Pan American Congress of Pediatrics will be held at Mexico City, Nov. 2, 3, 4, and 5, 1949, immediately following the Third National Congress on the three preceding days. Physicians who register become members of the congresses. Fee \$15.00 (U.S.A.) and for members of family \$8.00 for social activities. There will be a scientific exhibit and exhibits and films should be sent to the Organizing Committee at least a month before the Congress. Speakers at the plenary sessions are invited by the Committee. Members may present contributions (ten minutes) at the Sectional Sessions.

The program for the Pan American Congress is as follows:

*Tuesday, Nov. 1, 9 P.M.* Dinner given by the Mexican Society of Pediatrics.

*Wednesday, Nov. 2. First Plenary Session.*

9 A.M. "Acute Diarrheas in Infancy" Dr. Félix Hurtado (Cuba), Relator. Among the speakers will be Dr. Alexis Hartmann (U.S.A.), Dr. Frederick Tisdall (Canada), and Dr. Federico Gómez (Mexico).

11 A.M. "Hemolytic Syndromes of the Newborn." Among the speakers will be Dr. Louis K. Diamond (U.S.A.) and Dr. Juan P. Garrahan (Argentina).

3-6 P.M. Sectional meetings.

*Thursday, Nov. 3. Second Plenary Session.*

9 A.M. "Congenital Malformations of the Heart" Dr. Agustin Castellanos (Cuba), Relator. Among the speakers will be Dr. Rodolfo O. Kreutzer (Argentina), Dr. Antonio Prado Vértiz (Mexico), and Dr. Eugenio Tousaint (Mexico).

11 P.M. "B.C.G. Vaccination in America." Among the speakers will be Dr. S. R. Rosenthal (U.S.A.), Dr. José Bonaba (Uruguay), and Dr. Arlindo de Assis (Brazil).

3-6 P.M. Sectional meetings.

*Friday, Nov. 4. Third Plenary Session.*

9 A.M. "Pediatric Surgery." Among the speakers will be Dr. Herbert Coe (U.S.A.), Dr. Willis J. Potts (U.S.A.), and Dr. Jesús Lozoya Solís (Mexico).

11 A.M. "Virus Diseases in Pediatrics." Among the speakers will be Dr. Joseph Stokes, Jr. (U.S.A.), Dr. John A. Toomey (U.S.A.), and Dr. Rustin McIntosh (U.S.A.)

3-6 P.M. Sectional meetings.

*Saturday, Nov. 5. Fourth Plenary Session.*

9 A.M. "Child Neuropsychiatry." Among the speakers will be Dr. Florencio Escardó (Argentina) and Dr. Jorge Muñoz Turnbull (Mexico).

11 A.M. "Pediatrics in the Field of Social Security." Among the speakers will be Dr. Manuel Salcedo (Peru), Dr. Leslie Nelles Silverthorne (Canada), and Dr. John P. Hubbard (U.S.A.).

- 1 P.M. Banquet.  
4-7 P.M. Business and Closing Session.  
9 P.M. Dancing.

Full details may be obtained from the Secretary of the Second Pan American Congress, Dr. Alejandro Aguirre, Hospital Infantil, Mexico City, Mexico.

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#### Sixth International Congress of Pediatrics, Zurich, 1950.

1. It has been decided to hold the Congress during the last ten days of July, 1950. The actual Congress will last four to five days, July 24 to 28. It is proposed to hold two plenary sessions, each lasting one-half day, and a series of simultaneous group sessions. A plan for the group sessions has been drawn up, based on suggestions from all over the world.

Each group session will consist of prearranged lectures lasting from ten to thirty minutes, followed by open discussion in which no contribution may exceed five minutes. Proposals for important lectures not included in the program can only be accepted through the secretariats of the various national Pediatric Associations.

2. The manuscripts of lectures (without illustrations) must reach the Organizing Committee not later than April 1, 1950, to permit their being printed and issued to conference members in advance.

3. It is planned to hold a scientific exhibition lasting two weeks in a hall adjoining the Conference rooms to display the lecturers' curves, photographs, etc. The Organizing Committee will provide free of charge the exhibition space and cellotex sheets necessary to hang the curves. Showcases for diapositives, coloured photographs, etc., can only be provided if ordered and paid for well in advance. All those invited to lecture can display their material; other conference members must secure special permission from their national Pediatric Associations beforehand.

4. Those who wish to attend the Congress and those who plan to show an exhibit are requested to advise the Secretary of the Congress.

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Dr. Martha Eliot, Associate Chief of the Children's Bureau, has resigned to become Assistant Director General of the United Nations World Health Organization. Dr. Eliot, who has been associated with the Bureau for twenty-five years, will go to Geneva on June 1. Dr. Leona Baumgartner, Assistant Commissioner of Health for New York City, has been appointed to the Children's Bureau to fill Dr. Eliot's place on a six months' leave of absence from her present position.

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On April 5 the Alumni Association of the Children's Hospital, Washington, D. C., had its first meeting. About eighty-five former and present members of the house staff were present. Dr. Joseph S. Wall was elected president of the Association, Dr. Edgar P. Copeland vice-president, and Dr. Archibald R. MacPherson, 1220 W Street, N.W., secretary-treasurer. The Association is desirous of getting in touch with all former members of the staff.

## Book Reviews

**Safeguarding Motherhood.** Sol T. DeLee, M.D., Philadelphia, J. B. Lippincott Company, 135 pages. Price \$2.00.

The nephew of Joseph B. DeLee brings the famous obstetrical name to the field of prenatal care. The author has carefully solved the difficult problem of covering the prenatal subjects adequately in a short presentation. The various phases of conception, development of pregnancy, labor, and the post-partum period are treated in a simple, concise manner. An excellently presented section of the book deals with "Mental Attitudes and Beliefs," and will aid greatly in dispelling the superstitions and "old wives tales," with which every pregnant woman is besieged. There is a proper emphasis upon a well-balanced but controlled diet and a controlled weight gain during pregnancy. Certainly the advice given in this chapter could be taken as well by many obstetricians as by their patients.

Discussion of the various common disorders and also the more serious complications is brief and may be criticized by the generality that a little knowledge is a dangerous thing. Perhaps patients are unnecessarily disturbed mentally by imagining many symptoms and we question the advisability of attempting to explain these complications. The glossary contains technical terms probably unfamiliar to the mother and greatly increases the patient's understanding of the subjects discussed. G. J. L. WULFF, JR.

**Fetal and Neonatal Death.** Edith L. Potter, M.D., and Fred L. Adair, M.D., Chicago, 1949, University of Chicago Press, 174 pages. Price \$3.75.

A second revised edition of this well-known text published in 1939. The new edition not only brings the statistical portion up to a recent date, but there are many changes in the text in keeping with medical developments as the Rh factor. Like the first edition, the book is definitive in its field.

**The Oculorotary Muscles.** Richard A. Scobee, M.D., St. Louis, 1947, The C. V. Mosby Company, 359 pages.

**Strabismus, A Clinical Handbook.** George J. Epstein, M.D., Philadelphia, 1948, The Blakiston Company, 214 pages.

**The Management of Binocular Imbalance.** Emanuel Krinsky, M.D., Philadelphia, 1948, Lea & Febiger, 464 pages.

**Neurology of the Ocular Muscles.** David G. Cogan, M.D., Springfield, Ill., 1948, Charles C Thomas, 214 pages.

The appearance during the past year or so of these four books on the extraocular muscles is indicative of an accumulation of much new knowledge on this subject. The methods of examination have become much more detailed and accurate, resulting in exceedingly exact diagnoses. From a more expanded knowledge of visual physiology, especially in the fields of fusion and of suppression, a more accurate idea of the mechanism behind strabismus has developed. Finally, in the field of treatment there has been advance, not only in the surgical methods, but even more noteworthy in the rapidly advancing subject of orthoptic training.

All of these books are primarily for the ophthalmologist and are, therefore, quite technical in approach. The material and ideas of the authors differ in many aspects, but result in a satisfactory coverage of the subject. Although ophthalmologic in character, these books can give to the pediatrician an adequate idea of the fundamentals of this subject which is so necessary if the patient is to get the best final visual and cosmetic result.

All the material presented in these books gives emphasis to the modern concept of very early, complete, and energetic ophthalmic treatment in these cases. SANDERS.

## Editor's Column

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### ACCIDENTS

THE increasing importance of accidents as a major cause of death in childhood has been referred to editorially in THE JOURNAL previously. We have a great deal to learn about accidents, and hence information as to the age distribution, place, cause and character of the accident and the like are important in any sound attempt to lower the accident rates. It is for this reason that we publish a three-month study of accidents occurring in children treated at St. Luke's Hospital in Bethlehem, Pa., a city of some 65,000 population. The period included three summer months, and a comparison with three winter months when many children are attending school would, in all probability, show many differences.

During this period 566 children under 18 years of age were treated at the hospital, or an average of over six each day. It is of interest that there were no fatalities, although eleven cases necessitated major surgical procedures. About one child in six, or an average of one a day, had to be admitted to the wards, where the patient remained on an average of between seven and eight days. Assuming the hospital cost was \$10.00 a day, we have calculated that the total cost for hospital care amounted to \$6,500 for the three months, to say nothing of the x-rays, dressings, penicillin, antitoxin, etc., for the outpatient cases. Thus we can estimate that it costs the hospitals, or someone, \$30,000 or more a year to take care of the children accidentally injured in Bethlehem. If we add to this the accident cases treated by private physicians the total cost would be much greater. We leave it to the reader to estimate the medical bill for children injured each year in the United States. It must be enormous. This aside from the many fatalities, and the permanent crippling of many children.

Several interesting facts are brought out in this study. One is the tendency for accidents to increase the latter part of the day. Another is the peak in the third year of life. The older practitioners will note the almost negligible number of accidents due to fireworks around the fourth of July. We recall when "the Fourth" strained the facilities of the receiving ward and hospital. Legislation banning firecrackers has largely wiped out this cause for accidents. How much more legislation can accomplish in further reducing the accident rate is problematical. We hazard the guess that in the future education as to the importance and causes of accidents will do more to lower the accident rate in childhood than legislation.

## DR. ELIOT AND THE CHILDREN'S BUREAU

THE retirement of Dr. Martha Eliot from the Children's Bureau calls for more than a mere news item. Her appointment to the World Health Organization as Assistant Director General is a tribute to her ability and energy and to the sincerity of her work over many years to provide better health for women and children. Many physicians and the JOURNAL have not at times seen eye to eye with her as chief medical officer of the bureau, to which she has been attached for nearly a quarter of a century. There have been no disagreements as to ends or purposes, but rather honest differences of opinion as to the best means and ways to reach the goal. Despite these disagreements there has always been the greatest respect for Dr. Eliot as a physician and as an individual.

The differences of opinion have developed in large part from the feeling that the Children's Bureau has been active in promulgating a kind of social and political philosophy which is not involved in the primary purpose of the bureau of bringing about better maternal and child health, as this is fundamentally a technical problem of medicine and education. How much of this policy has stemmed from Dr. Eliot, and how much of it from the "higher ups" is a question we are not in a position to answer, but her position as medical chief has, of necessity, involved her representing bureau policies to the medical profession. For some reason or other government bureaus of all kinds (as recently highlighted by the Hoover reports) tend gradually to overemphasize the importance of the bureau, to look upon the bureau as an end in itself rather than a means to an end, to assume the function of policy-making rather than of carrying out policy as formulated by the people. This does not mean that the Children's Bureau has not made sound contributions to the health of American children, and this we attribute in no small part to Dr. Eliot's influence and ability. We all wish her success in her new position.

B. S. V.

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